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(54) Title: METHODS FOR TREATING VIRAL INFECTION USING IL-28 AND IL-29

(57) Abstract: IL-28A, IL-28B, IL-29, and certain mutants thereof have been shown to have antiviral activity on a spectrum of viral species. Of particular interest is the antiviral activity demonstrated on viruses that infect liver, such as hepatitis B virus and hepatitis C virus. In addition, IL-28A, IL-28B, IL-29, and mutants thereof do not exhibit some of the antiproliferative activity on hematopoietic cells that is observed with interferon treatment. Without the immunosuppressive effects accompanying interferon treatment, IL-28A, IL-28B, and IL-29 will be useful in treating immunocompromised patients for viral infections.

A12 - 10/691,923

<u>Description</u>

5   METHODS FOR TREATING VIRAL INFECTION USING IL-28 AND IL-29

BACKGROUND OF THE INVENTION

Strategies for treating infectious disease often focus on ways to enhance immunity. For instance, the most common method for treating viral infection involves

10   prophylactic vaccines that induce immune-based memory responses. Another method for treating viral infection includes passive immunization via immunoglobulin therapy (Meissner, <u>J. Pediatr.</u> 124:S17-21, 1994). Administration of Interferon alpha (IFN-α) is another method for treating viral infections such as genital warts (Reichman et al., <u>Ann. Intern. Med.</u> 108:675-9, 1988) and chronic viral infections like hepatitis C virus (HCV)

15   (Davis et al., <u>New Engl. J. Med.</u> 339:1493-9, 1998) and hepatitis B virus (HBV). For instance, IFN-α and IFN-β are critical for inhibiting virus replication (reviewed by Vilcek et al., (Eds.), <u>Interferons and other cytokines. In Fields Fundamental Virology.</u>, 3rd ed., Lippincott-Raven Publishers Philadelphia, PA, 1996, pages 341-365). In response to viral infection, CD4+ T cells become activated and initiate a T-helper type I

20   (TH1) response and the subsequent cascade required for cell-mediated immunity. That is, following their expansion by specific growth factors like the cytokine IL-2, T-helper cells stimulate antigen-specific CD8+ T-cells, macrophages, and NK cells to kill virally infected host cells. Although oftentimes efficacious, these methods have limitations in clinical use. For instance, many viral infections are not amenable to vaccine

25   development, nor are they treatable with antibodies alone. In addition, IFN's are not extremely effective and they can cause significant toxicities; thus, there is a need for improved therapies.

Not all viruses and viral diseases are treated identically because factors, such as whether an infection is acute or chronic and the patient's underlying health,

30   influence the type of treatment that is recommended. Generally, treatment of acute infections in immunocompetent patients should reduce the disease's severity, decrease complications, and decrease the rate of transmission. Safety, cost, and convenience are essential considerations in recommending an acute antiviral agent. Treatments for chronic infections should prevent viral damage to organs such as liver, lungs, heart,

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central nervous system, and gastrointestinal sytem, making efficacy the primary consideration.

Chronic hepatitis is one of the most common and severe viral infections of humans worldwide belonging to the *Hepadnaviridae* family of viruses. Infected
5   individuals are at high risk for developing liver cirrhosis, and eventually, hepatic cancer. Chronic hepatitis is characterized as an inflammatory liver disease continuing for at least six months without improvement. The majority of patients suffering from chronic hepatitis are infected with either chronic HBV, HCV or are suffering from autoimmune disease. The prevalence of HCV infection in the general population
10 exceeds 1% in the United States, Japan, China and Southeast Asia.

Chronic HCV can progress to cirrhosis and extensive necrosis of the liver. Although chronic HCV is often associated with deposition of type I collagen leading to hepatic fibrosis, the mechanisms of fibrogenesis remain unknown. Liver (hepatic) fibrosis occurs as a part of the wound-healing response to chronic liver injury.
15 Fibrosis occurs as a complication of haemochromatosis, Wilson's disease, alcoholism, schistosomiasis, viral hepatitis, bile duct obstruction, toxin exposure, and metabolic disorders. This formation of scar tissue is believed to represent an attempt by the body to encapsulate the injured tissue. Liver fibrosis is characterized by the accumulation of extracellular matrix that can be distinguished qualitatively from that in normal liver.
20 Left unchecked, hepatic fibrosis progresses to cirrhosis (defined by the presence of encapsulated nodules), liver failure, and death.

There are few effective treatments for hepatitis. For example, treatment of autoimmune chronic hepatitis is generally limited to immunosuppressive treatment with corticosteroids. For the treatment of HBV and HCV, the FDA has approved
25 administration of recombinant IFN-α. However, IFN-α is associated with a number of dose-dependent adverse effects, including thrombocytopenia, leukopenia, bacterial infections, and influenza-like symptoms. Other agents used to treat chronic HBV or HCV include the nucleoside analog RIBAVIRIN™ and ursodeoxycholic acid; however, neither has been shown to be very effective. RIBAVIRIN™ + IFN combination therapy
30 for results in 47% rate of sustained viral clearance (Lanford, R.E. and Bigger, C. Virology 293: 1-9 (2002). (See Medicine, (D. C. Dale and D. D. Federman, eds.) (Scientific American, Inc., New York), 4:VIII:1-8 (1995)).

Respiratory syncytial virus is the major cause of pneumonia and bronchiolitis in infancy. RSV infects more than half of infants during their first year of
35 exposure, and nearly all are infected after a second year. During seasonal epidemics most infants, children, and adults are at risk for infection or reinfection. Other groups at

risk for serious RSV infections include premature infants, immune compromised
children and adults, and the elderly. Symptoms of RSV infection range from a mild
cold to severe bronchiolitis and pneumonia. Respiratory syncytial virus has also been
associated with acute otitis media and RSV can be recovered from middle ear fluid.
Herpes simplex virus-1 (HSV-1) and herpes simplex virus-2 (HSV-2) may be either
lytic or latent, and are the causative agents in cold sores (HSV-1) and genital herpes,
typically associated with lesions in the region of the eyes, mouth, and genitals (HSV-2).
These viruses are a few examples of the many viruses that infect humans for which
there are few adequate treatments available once infection has occurred.

The demonstrated activities of the IL-28 and IL-29 cytokine family
provides methods for treating specific viral infections, in particular, liver specific viral
infections. The activity of IL-28 and IL-29 also demonstrate that these cytokines
provide methods for treating immunocompromised patients. The methods for these and
other uses that should be apparent to those skilled in the art from the teachings herein.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides methods for treating viral
infections comprising administering to a mammal with a viral infection causing liver
inflammation a therapeutically effective amount of a polypeptide comprising an amino
acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue
22 to residue 205, wherein after administration of the polypeptide the viral infection
level or liver inflammation is reduced. In other embodiments, the methods comprise
administering polypeptide comprising an amino acid sequence as shown in SEQ ID
NO:18, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, or SEQ ID
NO:36. In other embodiments, the polypeptide is conjugated to a polyalkyl oxide
moiety, such as PEG. In another embodiment, a reduction in the viral infection level is
measured as a decrease in viral load, an increase in antiviral antibodies, a decrease in
serological levels of alanine aminotransferase or histological improvement. In another
embodiment, the mammal is a human. In another embodiment, the present invention
provides that the viral infection is a hepatitis B virus infection or a hepatitis C virus
infection.

In another aspect, the present invention provides methods of treating a
viral infection comprising administering to a mammal with a viral infection causing
liver inflammation a therapeutically effective amount of polypeptide comprising an
amino acid sequence that has at least 95% identity to SEQ ID NO:4 from amino acid
residue 20 to residue 200, wherein after administration of the polypeptide the viral

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infection is reduced. In another embodiments, the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:20, SEQ ID NO:32, SEQ ID NO:34, or SEQ ID NO:38. In another embodiment, the polypeptide is conjugated to a polyalkyl oxide moiety, such as PEG. In another embodiment, the reduction in the viral infection levels
5   is measured as a decrease in viral load, an increase in antiviral antibodies, a decrease in serological levels of alanine aminotransferase or histological improvement. In another embodiment, the mammal is a human. In another embodiment, the viral infection is a hepatitis B virus infection or a hepatitis C virus infection.

In another aspect, the present invention provides methods for treating
10   liver inflammation comprising administering to a mammal in need thereof a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue 22 to residue 205, wherein after administration of the polypeptide the liver inflammation is reduced. In one embodiment, the invention provides that the polypeptide comprises an amino
15   acid sequence as shown in SEQ ID NO:18, SEQ ID NO:28, SEQ ID NO:30; SEQ ID NO:24, SEQ ID NO:26 or SEQ ID NO:36. In another embodiment, the polypeptide is conjugated to a polyalkyl oxide moiety, such as PEG. In another embodiment, the present invention provides that the reduction in the liver inflammation is measured as a decrease in serological level of alanine aminotransferase or histological improvement.
20   In another embodiment, the mammal is a human. In another embodiment, the liver inflammation is associated with a hepatitis C virus infection or a hepatitis B virus infection.

In another aspect, the present invention provides methods of treating a viral infection comprising administering to an immunocompromised mammal with an
25   viral infection a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue 22 to amino acid residue 205, wherein after administration of the polypeptide the viral infection is reduced. In another embodiment, the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:18, SEQ ID NO:28, SEQ ID NO:30; SEQ ID NO:24,
30   SEQ ID NO:26 or SEQ ID NO:36. In another embodiment, the polypeptide is conjugated to a polyalkyl oxide moiety, such as PEG. In another embodiment, a reduction in the viral infection level is measured as a decrease in viral load, an increase in antiviral antibodies, a decrease in serological levels of alanine aminotransferase or histological improvement. In another embodiment, the mammal is a human. In another
35   embodiment, the present invention provides that the viral infection is a hepatitis B virus infection or a hepatitis C virus infection.

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In another aspect, the present invention provides methods of treating a viral infection comprising administering to an immunocompromised mammal with a viral infection a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:4 from amino acid residue
5   20 to residue 200, wherein after administration of the polypeptide the viral infection is reduced. In other embodiments, the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:20, SEQ ID NO:32, SEQ ID NO:34, or SEQ ID NO:38. In another embodiment, the polypeptide is conjugated to a polyalkyl oxide moiety, such as PEG. In another embodiment, the reduction in the viral infection levels is measured as
10   a decrease in viral load, an increase in antiviral antibodies, a decrease in serological levels of alanine aminotransferase or histological improvement. In another embodiment, the mammal is a human. In another embodiment, the viral infection is a hepatitis B virus infection or a hepatitis C virus infection.

In another aspect, the present invention provides methods of treating
15   liver inflammation comprising administering to an immunocompromised mammal with liver inflammation a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue 22 to amino acid residue 205, wherein after administration of the polypeptide the liver inflammation is reduced. In another embodiment, the polypeptide comprises
20   an amino acid sequence as shown in SEQ ID NO:18, SEQ ID NO:28, SEQ ID NO:30; SEQ ID NO:24, SEQ ID NO:26 or SEQ ID NO:36. In another embodiment, the polypeptide is conjugated to a polyalkyl oxide moiety, such as PEG. In another embodiment, a reduction in the liver inflammation level is measured as a decrease in serological levels of alanine aminotransferase or histological improvement. In another
25   embodiment, the mammal is a human. In another embodiment, the present invention provides that the viral infection is a hepatitis B virus infection or a hepatitis C virus infection.

In another aspect, the present invention provides methods of treating liver inflammation comprising administering to an immunocompromised mammal with
30   liver inflammation a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:4 from amino acid residue 20 to residue 200, wherein after administration of the polypeptide the liver inflammation is reduced. In other embodiments, the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:20, SEQ ID NO:32, SEQ ID NO:34, or SEQ ID
35   NO:38. In another embodiment, the polypeptide is conjugated to a polyalkyl oxide moiety, such as PEG. In another embodiment, the reduction in the liver inflammation

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is measured as a decrease in serological levels of alanine aminotransferase or histological improvement. In another embodiment, the mammal is a human. In another embodiment, the viral infection is a hepatitis B virus infection or a hepatitis C virus infection.

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DESCRIPTION OF THE INVENTION

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

10   The term "affinity tag" is used herein to denote a polypeptide segment that can be attached to a second polypeptide to provide for purification or detection of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-

15   histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-4, 1985), substance P, Flag™ peptide (Hopp et al., Biotechnology 6:1204-10, 1988), streptavidin binding peptide, or other antigenic epitope or binding domain. See, in

20   general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. DNAs encoding affinity tags are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation

25   arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to

30   denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete

35   polypeptide.

The term "complement/anti-complement pair" denotes non-identical moieties that form a non-covalently associated, stable pair under appropriate conditions. For instance, biotin and avidin (or streptavidin) are prototypical members of a complement/anti-complement pair. Other exemplary complement/anti-complement pairs include receptor/ligand pairs, antibody/antigen (or hapten or epitope) pairs, sense/antisense polynucleotide pairs, and the like. Where subsequent dissociation of the complement/anti-complement pair is desirable, the complement/anti-complement pair preferably has a binding affinity of $<10^9$ M^{-1}.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons contain different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, Nature 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide is substantially free of other polypeptides, particularly other polypeptides of animal origin. It is preferred to provide the polypeptides in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude

the presence of the same polypeptide in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

The term "level" when referring to immune cells, such as NK cells, T cells, in particular cytotoxic T cells, B cells and the like, an increased level is either increased number of cells or enhanced activity of cell function.

The term "level" when referring to viral infections refers to a change in the level of viral infection and includes, but is not limited to, a change in the level of CTLs or NK cells (as described above), a decrease in viral load, an increase antiviral antibody titer, decrease in serological levels of alanine aminotransferase, or improvement as determined by histological examination of a target tissue or organ. Determination of whether these changes in level are significant differences or changes is well within the skill of one in the art.

The term "operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator.

The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example, α-globin, β-globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized in vitro, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

The term "receptor" denotes a cell-associated protein that binds to a bioactive molecule (i.e., a ligand) and mediates the effect of the ligand on the cell. Membrane-bound receptors are characterized by a multi-peptide structure comprising an extracellular ligand-binding domain and an intracellular effector domain that is typically involved in signal transduction. Binding of ligand to receptor results in a conformational change in the receptor that causes an interaction between the effector domain and other molecule(s) in the cell. This interaction in turn leads to an alteration in the metabolism of the cell. Metabolic events that are linked to receptor-ligand interactions include gene transcription, phosphorylation, dephosphorylation, increases in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. In general, receptors can be membrane bound, cytosolic or nuclear; monomeric (e.g., thyroid stimulating hormone receptor, beta-adrenergic receptor) or multimeric (e.g., PDGF receptor, growth hormone receptor, IL-3 receptor, GM-CSF receptor, G-CSF receptor, erythropoietin receptor and IL-6 receptor).

The term "secretory signal sequence" denotes a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The term "splice variant" is used herein to denote alternative forms of RNA transcribed from a gene. Splice variation arises naturally through use of

alternative splicing sites within a transcribed RNA molecule, or less commonly between separately transcribed RNA molecules, and may result in several mRNAs transcribed from the same gene. Splice variants may encode polypeptides having altered amino acid sequence. The term splice variant is also used herein to denote a

5   protein encoded by a splice variant of an mRNA transcribed from a gene.

Molecular weights and lengths of polymers determined by imprecise analytical methods (e.g., gel electrophoresis) will be understood to be approximate values. When such a value is expressed as "about" X or "approximately" X, the stated value of X will be understood to be accurate to ±10%.

10 "zcyto20", "zcyto21", "zcyto22" are the previous designations for human IL-28A, IL-29, and IL-28B. IL-28A nucleotide and amino acid sequences are shown in SEQ ID NOS: 1, 2, 17, 18, 35, 36. IL-28B nucleotide and amino acid sequences are shown in SEQ ID NOS: 5, 6, 21, 22, 39, 40. IL-29 nucleotide and amino acid sequences are shown in SEQ ID NOS: 3, 4, 19, 20, 37, 38. These sequences are

15 described in PCT application WO 02/086087 and U.S. Provisional Patent Application No. 60/493,194, both commonly assigned to ZymoGenetics, Inc., incorporated herein by reference.

"zcyto24" and "zcyto25" are the previous designations for mouse IL-28A and IL-28B, and are shown in SEQ ID NOS: 7, 8, 9, 10, respectively. The

20 polynucleotide and polypeptides are fully described in PCT application WO 02/086087 commonly assigned to ZymoGenetics, Inc., incorporated herein by reference.

"zcytor19" is the previous designation for IL-28 receptor α-subunit, and is shown in SEQ ID NOS: 11, 12, 13, 14, 15, 16. The polynucleotides and polypeptides are described in PCT application WO 02/20569 on behalf of Schering, Inc., and WO

25 02/44209 assigned to ZymoGenetics, Inc and incorporated herein by reference. "IL-28 receptor" denotes the IL-28 α-subunit and CRF2-4 subunit forming a heterodimeric receptor.

All references cited herein are incorporated by reference in their entirety.

30 We have previously reported the discovery of a new family of interferon-like molecules in PCT applications, PCT/US01/21087 and PCT/US02/12887, and Sheppard et al., Nature Immunol. 4:63-68, 2003; herein all incorporated by reference. This new family includes molecules designated zcyto20 (SEQ ID NOS: 1 and 2; 17 and 18), zcyto21 (SEQ ID NOS:3 and 4; 19 and 20), zcyto22 (SEQ ID NOS:5 and 6; 21 and

35 22), zcyto24 (SEQ ID NOS:7 and 8), zcyto25 (SEQ ID NOS: 9 and 10), where zcyto20, 21, and 22 are human sequences, and zcyto24 and 25 are mouse sequences. HUGO

designations have been assigned to the interferon-like proteins. Zcyto20 has been designated IL-28A, zycto22 has been designated IL-28B, zycto21 has been designated IL-29, and will be referred to by the HUGO names hereafter. Kotenko et al., Nature Immunol. 4:69-77, 2003, have identified IL-28A as IFNλ2, IL-28B as IFNλ3, and IL-29

5 as IFNλ1. The receptor for these proteins, originally designated zcytor19 (SEQ ID NOS: 11 and 12), has been designated as IL-28RA by HUGO.

The present invention provides methods for using IL-28 and IL-29 as an antiviral agent in a broad spectrum of viral infections. In certain embodiments, the methods include using IL-28 and IL-29 in viral infections that are specific for liver,

10 such as hepatitis. Furthermore, data indicate that IL-28 and IL-29 exhibit these antiviral activities without some of the toxicities associated with the use of IFN therapy for viral infection. One of the toxicities related to type I interferon therapy is myelosuppression. This is due to type I interferons suppression of bone marrow progenitor cells. Because IL-29 does not significantly suppress bone marrow cell expansion or B cell proliferation

15 as is seen with IFN-α, IL-29 will have less toxicity associated with treatment. Similar results would be expected with IL-28A and IL-28B.

IFN-α may be contraindicated in some patients, particularly when doses sufficient for efficacy have some toxicity or myelosuppressive effects. Examples of patients for which IFN is contraindicated can include (1) patients given previous

20 immunosuppressive medication, (2) patients with HIV or hemophilia, (3) patients who are pregnant, (4) patients with a cytopenia, such as leukocyte deficiency, neutropenia, thrombocytopenia, and (5) patients exhibiting increased levels of serum liver enzymes. Moreover, IFN therapy is associated with symptoms that are characterized by nausea, vomiting, diarrhea and anorexia. The result being that some populations of patients

25 will not tolerate IFN therapy, and IL-28A, IL-28B, and IL-29 can provide an alternative therapy for some of those patients.

The methods of the present invention comprise administering a therapeutically effective amount of IL-28A, IL-28B, IL-29, or mutant of said molecules that have retained some biological activity associated with IL-28A, IL-28B or IL-29,

30 alone or in combination with other biologics or pharmaceuticals. The present invention provides methods of treating a mammal with a chronic or acute viral infection, causing liver inflammation, thereby reducing the viral infection or liver inflammation. In another aspect, the present invention provides methods of treating liver specific diseases, in particular liver disease where viral infection is in part an etiologic agent.

35 These methods are based on the discovery that IL-28 and IL-29 have antiviral activity on hepatic cells.

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As stated above, the methods of the present invention provide administering a therapeutically effective amount of IL-28A, IL-28B, IL-29, or mutant of said molecules that have retained some biological activity associated with IL-28A, IL-28B or IL-29, alone or in combination with other biologics or pharmaceuticals. The present invention provides methods of treatment of a mammal with a viral infection selected from the group consisting of hepatitis A, hepatitis B, hepatitis C, and hepatitis D. Other aspects of the present invention provide methods for using IL-28 or IL-29 as an antiviral agent in viral infections selected from the group consisting of respiratory syncytial virus, herpes virus, Epstein-Barr virus, influenza virus, adenovirus, parainfluenza virus, rhino virus, coxsackie virus, vaccinia virus, west nile virus, dengue virus, venezuelan equine encephalitis virus, pichinde virus and polio virus. . In certain embodiments, the mammal can have either a chronic or acute viral infection.

In another aspect, the methods of the present invention also include a method of treating a viral infection comprising administering a therapeutically effective amount of IL-28A, IL-28B, IL-29, or mutant of said molecules that have retained some biological activity associated with IL-28A, IL-28B or IL-29, alone or in combination with other biologics or pharmaceuticals, to an immunompromised mammal with a viral infection, thereby reducing the viral infection, such as is described above. All of the above methods of the present invention can also comprise the administration of zcyto24 or zcyto25 as well.

A.   Description of IL-28A, IL-28B, and IL-29 Polynucleotides and Polypeptides

An IL-28A gene encodes a polypeptide of 205 amino acids, as shown in SEQ ID NO:2. The signal sequence for IL-28A comprises amino acid residue 1 (Met) through amino acid residue 21 (Ala) of SEQ ID NO:2. The mature peptide for IL-28A begins at amino acid residue 22 (Val). A variant IL-28A gene encodes a polypeptide of 200 amino acids, as shown in SEQ ID NO:18. The signal sequence for IL-28A can be predicted as comprising amino acid residue -25 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:18. The mature peptide for IL-28A begins at amino acid residue 1 (Val). IL-28A helices are predicted as follow: helix A is defined by amino acid residues 24 (Leu) to 40 (Glu); helix B by amino acid residues 58 (Thr) to 65 (Gln); helix C by amino acid residues 69 (Arg) to 85 (Ala); helix D by amino acid residues 95 (Val) to 114 (Ala); helix E by amino acid residues 126 (Thr) to 142 (Lys); and helix F by amino acid residues 148 (Cys) to 169 (Ala); as shown in SEQ ID NO: 18. When a polynucleotide sequence encoding the mature polypeptide is expressed in a prokaryotic system, such as *E. coli*, the a secretory signal sequence may not be required and the an

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N-terminal Met will be present, resulting in expression of a polypeptide such as is shown in SEQ ID NO:36.

     The IL-29 gene encodes a polypeptide of 200 amino acids, as shown in SEQ ID NO:4. The signal sequence for IL-29 comprises amino acid residue 1 (Met)

5   through amino acid residue 19 (Ala) of SEQ ID NO:4. The mature peptide for IL-29 begins at amino acid residue 20 (Gly). IL-29 has been described in published PCT application WO 02/02627. A variant IL-29 gene encodes a polypeptide of 200 amino acids, as shown in SEQ ID NO:20, where amino acid residue 169 is Asn instead of Asp. The signal sequence for IL-29 can be predicted as comprising amino acid residue -19

10 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:20. The mature peptide for IL-29 begins at amino acid residue 1 (Gly). IL-29 has been described in PCT application WO 02/02627. IL-29 helices are predicted as follows: helix A is defined by amino acid residues 30 (Ser) to 44 (Leu); helix B by amino acid residues 57 (Asn) to 65 (Val); helix C by amino acid residues 70 (Val) to 85 (Ala); helix D by amino acid

15 residues 92 (Glu) to 114 (Gln); helix E by amino acid residues 118 (Thr) to 139 (Lys); and helix F by amino acid residues 144 (Gly) to 170 (Leu); as shown in SEQ ID NO: 20. When a polynucleotide sequence encoding the mature polypeptide is expressed in a prokaryotic system, such as *E. coli*, the a secretory signal sequence may not be required and the an N-terminal Met will be present, resulting in expression of a polypeptide such

20 as is shown in SEQ ID NO:38.

     The IL-28B gene encodes a polypeptide of 205 amino acids, as shown in SEQ ID NO:6. The signal sequence for IL-28B comprises amino acid residue 1 (Met) through amino acid residue 21 (Ala) of SEQ ID NO:6. The mature peptide for IL-28B begins at amino acid residue 22 (Val). A variant IL-28B gene encodes a polypeptide of

25 200 amino acids, as shown in SEQ ID NO:22. The signal sequence for IL-28B can be predicted as comprising amino acid residue -21 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:22. The mature peptide for IL-28B begins at amino acid residue 1 (Val). IL-28B helices are predicted as follow: helix A is defined by amino acid residues 8 (Leu) to 41 (Glu); helix B by amino acid residues 58 (Trp) to 65 (Gln); helix C by

30 amino acid residues 69 (Arg) to 86 (Ala); helix D by amino acid residues 95 (Gly) to 114 (Ala); helix E by amino acid residues 126 (Thr) to 142 (Lys); and helix F by amino acid residues 148 (Cys) to 169 (Ala); as shown in SEQ ID NO: 2. When a polynucleotide sequence encoding the mature polypeptide is expressed in a prokaryotic system, such as *E. coli*, the a secretory signal sequence may not be required and the an

35 N-terminal Met will be present, resulting in expression of a polypeptide such as is shown in SEQ ID NO:40.

14

Zcyto24 gene encodes a polypeptide of 202 amino acids, as shown in SEQ ID NO:8. Zcyto24 secretory signal sequence comprises amino acid residue 1 (Met) through amino acid residue 28 (Ala) of SEQ ID NO:8. An alternative site for cleavage of the secretory signal sequence can be found at amino acid residue 24 (Thr).
5   The mature polypeptide comprises amino acid residue 29 (Asp) to amino acid residue 202 (Val).

Zcyto25 gene encodes a polypeptide of 202 amino acids, as shown in SEQ ID NO:10. Zcyto25 secretory signal sequence comprises amino acid residue 1 (Met) through amino acid residue 28 (Ala) of SEQ ID NO:10. An alternative site for
10 cleavage of the secretory signal sequence can be found at amino acid residue 24 (Thr). The mature polypeptide comprises amino acid residue 29 (Asp) to amino acid residue 202 (Val).

The present invention provides methods comprising administration of polypeptides having mutations in the IL-28 and IL-29 wildtype sequence that result in
15 expression of single forms of the IL-28 or IL-29 molecule. Exemplary mutants are shown in SEQ ID NOS: 24, 28, and 32. When IL-28 and IL-29 are expressed in *E. coli*, an N-terminal Methionine is present. SEQ ID NOS: 26, 30 and 34 show the amino acid residue numbering for IL-28A and IL-29 mutants when the N-terminal Met is present. Table 1 shows the possible combinations of intramolecular disulfide bonded cysteine
20 pairs for wildtype IL-28A, IL-28B, and IL-29.

15

Table 1

IL-28A SEQ ID NO:18	C_{16}-C_{115}	C_{48}-C_{148}	C_{50}-C_{148}	C_{167}-C_{174}	C_{16}-C_{48}	C_{16}-C_{50}	C_{48}-C_{115}	C_{50}-C_{115}	C_{115}-C_{148}
Met IL-28A SEQ ID NO:36	C_{17}-C_{116}	C_{49}-C_{149}	C_{51}-C_{1498}	C_{168}-C_{175}	C_{17}-C_{49}	C_{17}-C_{51}	C_{49}-C_{116}	C_{51}-C_{116}	C_{116}-C_{149}
IL-29 SEQ ID NO:20	C_{15}-C_{112}	C_{49}-C_{145}	C_{112}-C_{171}						
Met IL-29 SEQ ID NO:38	C_{16}-C_{113}	C_{50}-C_{146}	C_{113}-C_{172}						
IL-28B SEQ ID NO:22	C_{16}-C_{115}	C_{48}-C_{148}	C_{50}-C_{148}	C_{167}-C_{174}	C_{16}-C_{48}	C_{16}-C_{50}	C_{48}-C_{115}	C_{50}-C_{115}	C_{115}-C_{148}
Met IL-28B SEQ ID NO:40	C_{17}-C_{116}	C_{49}-C_{149}	C_{51}-C_{1498}	C_{168}-C_{175}	C_{17}-C_{49}	C_{17}-C_{51}	C_{49}-C_{116}	C_{51}-C_{116}	C_{116}-C_{149}

Conjugation of interferons with water-soluble polymers has been shown to enhance the circulating half-life of the interferon, and to reduce the immunogenicity of the polypeptide (see, for example, Nieforth et al., Clin. Pharmacol. Ther. 59:636 (1996), and Monkarsh et al., Anal. Biochem. 247:434 (1997)). Suitable water-soluble polymers include polyethylene glycol (PEG), monomethoxy-PEG, mono-(C1-C10)alkoxy-PEG, aryloxy-PEG, poly-(N-vinyl pyrrolidone)PEG, tresyl monomethoxy PEG, PEG propionaldehyde, bis-succinimidyl carbonate PEG, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, dextran, cellulose, or other carbohydrate-based polymers. Suitable PEG may have a molecular weight from about 600 to about 60,000, including, for example, 5,000, 12,000, 20,000 and 40,000. A Cysteine mutant IL-28 or IL-29 conjugate can also comprise a mixture of such water-soluble polymers.

One example of a IL-28 or IL-29 conjugate comprises a IL-28 or IL-29 moiety, or mutant thereof, and a polyalkyl oxide moiety attached to the N-terminus of the IL-28 or IL-29 moiety. PEG is one suitable polyalkyl oxide. As an illustration, IL-

28 or IL-29 can be modified with PEG, a process known as "PEGylation." PEGylation of IL-28 or IL-29 can be carried out by any of the PEGylation reactions known in the art (see, for example, EP 0 154 316, Delgado *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems 9:249 (1992), Duncan and Spreafico, Clin. Pharmacokinet. 27:290

5   (1994), and Francis *et al.*, Int J Hematol 68:1 (1998)). The methods of the present invention include administration of IL-28, IL-29, and mutants thereof conjugated to water-soluble polymers, such as PEG.

IL-28A, IL-29, IL-28B, zcyto24 and zcyto25, each have been shown to form a complex with the orphan receptor designated zcytor19 (IL-28RA). IL-28RA is

10   described in a commonly assigned patent application PCT/US01/44808. IL-28B, IL-29, zcyto24, and zcyto25 have been shown to bind or signal through IL-28RA as well, further supporting that IL-28A, IL-29, IL-28B, zcyto24 and zcyto25 are members of the same family of cytokines. IL-28RA receptor is a class II cytokine receptor. Class II cytokine receptors usually bind to four-helix-bundle cytokines. For example,

15   interleukin-10 and the interferons bind receptors in this class (e.g., interferon-gamma receptor, alpha and beta chains and the interferon-alpha/beta receptor alpha and beta chains).

Class II cytokine receptors are characterized by the presence of one or more cytokine receptor modules (CRM) in their extracellular domains. Other class II

20   cytokine receptors include zcytor11 (commonly owned US Patent No. 5,965,704), CRF2-4 (Genbank Accession No. Z17227), IL-10R (Genbank Accession No.s U00672 and NM_001558), DIRS1, zcytor7 (commonly owned US Patent No. 5,945,511), and tissue factor. IL-28RA, like all known class II receptors except interferon-alpha/beta receptor alpha chain, has only a single class II CRM in its extracellular domain.

25   Analysis of a human cDNA clone encoding IL-28RA (SEQ ID NO:11) revealed an open reading frame encoding 520 amino acids (SEQ ID NO:12) comprising a secretory signal sequence (residues 1 (Met) to 20 (Gly) of SEQ ID NO:12) and a mature IL-28RA cytokine receptor polypeptide (residues 21 (Arg) to 520 (Arg) of SEQ ID NO:12) an extracellular ligand-binding domain of approximately 206 amino acid

30   residues (residues 21 (Arg) to 226 (Asn) of SEQ ID NO:12), a transmembrane domain of approximately 23 amino acid residues (residues 227 (Trp) to 249 (Trp) of SEQ ID NO:12), and an intracellular domain of approximately 271 amino acid residues (residues 250 (Lys) to 520 (Arg) of SEQ ID NO:12). Within the extracellular ligand-binding domain, there are two fibronectin type III domains and a linker region. The

35   first fibronectin type III domain comprises residues 21 (Arg) to 119 (Tyr) of SEQ ID NO:12, the linker comprises residues 120 (Leu) to 124 (Glu) of SEQ ID NO:12, and the

second fibronectin type III domain comprises residues 125 (Pro) to 223 (Pro) of SEQ ID NO:12.

In addition, a human cDNA clone encoding a IL-28RA variant with a 29 amino acid deletion was identified. This IL-28RA variant (as shown in SEQ ID NO:13)
5   comprises an open reading frame encoding 491 amino acids (SEQ ID NO:14) comprising a secretory signal sequence (residues 1 (Met) to 20 (Gly) of SEQ ID NO:14) and a mature IL-28RA cytokine receptor polyptide (residues 21 (Arg) to 491 (Arg) of SEQ ID NO:14) an extracellular ligand-binding domain of approximately 206 amino acid residues (residues 21 (Arg) to 226 (Asn) of SEQ ID NO:14, a transmembrane
10   domain of approximately 23 amino acid residues (residues 227 (Trp) to 249 (Trp) of SEQ ID NO:14), and an intracellular domain of approximately 242 amino acid residues (residues 250 (Lys) to 491 (Arg) of SEQ ID NO:14).

A truncated soluble form of the IL-28RA receptor mRNA appears to be naturally expressed. Analysis of a human cDNA clone encoding the truncated soluble
15   IL-28RA (SEQ ID NO:15) revealed an open reading frame encoding 211 amino acids (SEQ ID NO:16) comprising a secretory signal sequence (residues 1 (Met) to 20 (Gly) of SEQ ID NO:16) and a mature truncated soluble IL-28RA receptor polyptide (residues 21 (Arg) to 211 (Ser) of SEQ ID NO:16) a truncated extracellular ligand-binding domain of approximately 143 amino acid residues (residues 21 (Arg) to 163
20   (Trp) of SEQ ID NO:16), no transmembrane domain, but an additional domain of approximately 48 amino acid residues (residues 164 (Lys) to 211 (Ser) of SEQ ID NO:16).

IL-28RA is a member of the same receptor subfamily as the class II cytokine receptors, and receptors in this subfamily may associate to form homodimers
25   that transduce a signal. Several members of the subfamily (e.g., receptors that bind interferon, IL-10, IL-19, and IL-TIF) combine with a second subunit (termed a β-subunit) to bind ligand and transduce a signal. However, in many cases, specific β-subunits associate with a plurality of specific cytokine receptor subunits. For example, class II cytokine receptors, such as, zcytor11 (US Patent No. 5,965,704) and CRF2-4
30   receptor heterodimerize to bind the cytokine IL-TIF (See, WIPO publication WO 00/24758; Dumontier et al., J. Immunol. 164:1814-1819, 2000; Spencer, SD et al., J. Exp. Med. 187:571-578, 1998; Gibbs, VC and Pennica Gene 186:97-101, 1997 (CRF2-4 cDNA); Xie, MH et al., J. Biol. Chem. 275: 31335-31339, 2000). IL-10β receptor is believed to be synonymous with CRF2-4 (Dumoutier, L. et al., Proc. Nat'l. Acad. Sci.
35   97:10144-10149, 2000; Liu Y et al, J Immunol. 152; 1821-1829, 1994 (IL-10R cDNA). Therefore, one could expect that zcyto20, zcyto21, zcyto22, zcyto24 and zcyto25 would

bind either monomeric, homodimeric, heterodimeric and multimeric zcytor19 receptors. Experimental evidence has identified CRF2-4 as the putative binding partner for IL-28RA.

Examples of biological activity for molecules used to identify IL-28 or
5   IL-29 molecules that are useful in the methods of the present invention include molecules that can bind to the IL-28 receptor with some specificity. Generally, a ligand binding to its cognate receptor is specific when the K_D falls within the range of 100 nM to 100 pM. Specific binding in the range of 100 mM to 10 nM K_D is low affinity binding. Specific binding in the range of 2.5 pM to 100 pM K_D is high affinity binding.
10   In another example, biologically active IL-28 or IL-29 molecules are capable of some level of antiviral activity associated with wildtype IL-28 or IL-29.

B.   Use of IL-28A, IL-28B, and IL-29 for Viral Infections

IL-28 and IL-29 can be used in treating liver specific diseases, in
15   particular liver disease where viral infection is in part an etiologic agent. In particular IL-28 and IL-29 will be used to treat a mammal with a viral infection selected from the group consisting of hepatitis A, hepatitis B, hepatitis C, and hepatitis D. When liver disease is inflammatory and continuing for at least six months, it is generally considered chronic hepatitis. Hepatitis C virus (HCV) patients actively infected will be
20   positive for HCV-RNA in their blood, which is detectable by reverse transcritptase/polymerase chain reaction (RT-PCR) assays. The methods of the present invention will slow the progression of the liver disease. Clinically, diagnostic tests for HCV include serologic assays for antibodies and molecular tests for viral particles. Enzyme immunoassays are available (Vrielink et al., Transfusion 37:845-849, 1997),
25   but may require confirmation using additional tests such as an immunoblot assay (Pawlotsky et al., Hepatology 27:1700-1702, 1998). Qualitative and quantitative assays generally use polymerase chain reaction techniques, and are preferred for assessing viremia and treatment response (Poynard et al., Lancet 352:1426-1432, 1998; McHutchinson et al., N. Engl. J. Med. 339:1485-1492, 1998). Several commercial tests
30   are available, such as, quantitative RT-PCR (Amplicor HCV Monitor™, Roche Molecular Systems, Branchburg, NJ) and a branched DNA (deoxyribonucleic acid) signal amplification assay (Quantiplex™ HCV RNA Assay [bDNA], Chiron Corp., Emeryville, CA). A non-specific laboratory test for liver inflammation or necrosis measures alanine aminotransferase level (ALT) and is inexpensive and readily available
35   (National Institutes of Health Consensus Development Conference Panel, Hepatology 26 (Suppl. 1):2S-10S, 1997). Histologic evaluation of liver biopsy is generally

considered the most accurate means for determining hepatitis progression (Yano et al., Hepatology 23:1334-1340, 1996.) For a review of clinical tests for HCV, see, Lauer et al., N. Engl. J. Med. 345:41-52, 2001.

There are several *in vivo* models for testing HBV and HCV that are
5   known to those skilled in art. For example, the effects of IL-28 or IL-29 on mammals infected with HBV can accessed using a woodchuck model. Briefly, woodchucks chronically infected with woodchuck hepatitis virus (WHV) develop hepatitis and hepatocellular carcinoma that is similar to disease in humans chronically infected with HBV. The model has been used for the preclinical assessment of antiviral activity. A
10 chronically infected WHV strain has been established and neonates are inoculated with serum to provide animals for studying the effects of certain compounds using this model. (For a review, see, Tannant et al., ILAR J. 42 (2):89-102, 2001). Chimpanzees may also be used to evaluate the effect of IL-28 and IL-29 on HBV infected mammals. Using chimpanzees, characterization of HBV was made and these studies demonstrated
15 that the chimpanzee disease was remarkably similar to the disease in humans (Barker et al., J. Infect. Dis. 132:451-458, 1975 and Tabor et al., J. Infect. Dis. 147:531-534, 1983.) The chimpanzee model has been used in evaluating vaccines (Prince et al., In: Vaccines 97, Cold Spring Harbor Laboratory Press, 1997.) Therapies for HIV are routinely tested using non-human primates infected with simian immunodeficiency
20 viruses (for a review, see, Hirsch et al., Adv. Pharmcol. 49:437-477, 2000 and Nathanson et al., AIDS 13 (suppl. A):S113-S120, 1999.) For a review of use of non-human primates in HIV, hepatitis, malaria, respiratory syncytial virus, and other diseases, see, Sibal et al., ILAR J. 42 (2):74-84, 2001.

Other examples of the types of viral infections for which IL-28A, IL-
25 28B, and IL-29 can be useful include, but are not limited to: infections caused by DNA Viruses (e.g., Herpes Viruses such as Herpes Simplex viruses, Epstein-Barr virus, Cytomegalovirus; Pox viruses such as Variola (small pox) virus; Hepadnaviruses (e.g, Hepatitis B virus); Papilloma viruses; Adenoviruses); RNA Viruses (e.g., HIV I, II; HTLV I, II; Poliovirus; Hepatitis A; Orthomyxoviruses (e.g., Influenza viruses);
30 Paramyxoviruses (e.g., Measles virus); Rabies virus; Hepatitis C); Rhinovirus, Respiratory Syncytial Virus, West Nile Virus, Yellow Fever, Rift Vallley Virus, Lassa Fever Virus, Ebola Virus, Lymphocytic Choriomeningitis Virus, which replicates in tissues including liver, and the like. Moreover, examples of the types of diseases for which IL-28 and IL-29 could be used include, but are not limited to: Acquired
35 immunodeficiency; Hepatitis; Gastroenteritis; Hemorrhagic diseases; Enteritis; Carditis; Encephalitis; Paralysis; Brochiolitis; Upper and lower respiratory disease; Respiratory

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Papillomatosis; Arthritis; Disseminated disease, hepatocellular carcinoma resulting rom chronic Hepatitis C infection. In addition, viral disease in other tissues may be treated with IL-28A, IL-28B, and IL-29, for example viral meningitis, and HIV-related disease. For example, a transgenic model for testing the activity of a therapeutic sample is
5   described in the following examples and described in Morrey, et al., Antiviral Ther., 3 (Suppl 3):59-68, 1998.

Animal models that are used to test for efficacy in specific viruses are known. For example, Dengue Virus can be tested using a model as such as described in Huang et al., J. Gen. Virol. Sep;81(Pt 9):2177-82, 2000. West Nile Virus can be tested
10   using the model as described in Xiao et al., Emerg. Infect. Dis. Jul-Aug;7(4):714-21, 2001or Mashimo et al., Proc. Natl. Acad. Sci. U S A. Aug 20;99(17):11311-6, 2002. Venezuelan equine encephalitis virus model is described in Jackson et al., Veterinary Pathology, 28 (5): 410-418, 1991; Vogel et al., Arch. Pathol. Lab. Med. Feb;120(2):164-72, 1996; Lukaszewski and Brooks, J. of Virology, 74(11):5006-5015,
15   2000. Rhinoviruses models are described in Yin and Lomax, J. Gen. Virol. 67 (Pt 11):2335-40, 1986. Models for respiratory syncytial virus are described in Byrd and Prince, Clin. Infect. Dis. 25(6):1363-8, 1997. Other models are known in the art and it is well within the skill of those ordinarily skilled in the art to know how to use such models.

20   IL-28A, IL-28B, and IL-29 can be used in combination with antiviral agents, including those described above. Some of the more common treatments for viral infection include drugs that inhibit viral replication such as ACYCLOVIR™. In addition, the combined use of some of these agents form the basis for highly active antiretroviral therapy (HAART) used for the treatment of AIDS. Examples in which
25   the combination of immunotherapy (i.e. cytokines) and antiviral drugs shows improved efficacy include the use of interferon plus RIBAVIRIN™ for the treatment of chronic hepatitis C infection (Maddrey, Semin. Liver. Dis.19 Suppl 1:67-75, 1999) and the combined use of IL-2 and HAART (Ross, et al, ibid..) Thus, as IL-28 and IL-29 can stimulate the immune system against disease, it can similarly be used in HAART
30   applications.

In particular, IL-28A, IL-28B, and IL-29 may be useful in monotherapy or combination therapy with IFN-α (with or without RIBAVIRIN™) in patients who do not respond well to IFN therapy. These patients may not respond to IFN therapy due to having less type I interferon receptor on the surface of their cells (Yatsuhashi H, et al., J
35   Hepatol. Jun.30(6):995-1003, 1999; Mathai et al., J Interferon Cytokine Res. Sep.19(9):1011-8, 1999; Fukuda et al., J Med. Virol. 63(3):220-7, 2001). IL-28A, IL-

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28B, and IL-29 may also be useful in monotherapy or combination therapy with IFN-α (with or without RIBAVIRIN™) in patients who have less type I interferon receptor on the surface of their cells due to down-regulation of the type I interferon receptor after type I interferon treatment (Dupont et al., J. Interferon Cytokine Res. 22(4):491-501,

5   2002).

IL-28 or IL-29 can be used in combination with other immunotherapies including cytokines, immunoglobulin transfer, and various co-stimulatory molecules. In addition to antiviral drugs, IL-28, IL-29, or mutants thereof could be used in combination with any other immunotherapy that is intended to stimulate the immune

10   system. Thus, IL-28, IL-29, or mutants thereof could be used with other cytokines such as Interferon or IL-2. IL-28, IL-29, or mutants thereof could also be added to methods of passive immunization that involve immunoglobulin transfer, one example bring the use of antibodies to treat RSV infection in high risk patients (Meissner HC, ibid.). In addition, IL-28, IL-29, or mutants thereof could be used with additional co-stimulatory

15   molecules such as 4-1BB ligand that recognize various cell surface molecules like CD137 (Tan, JT et al., J Immunol. 163:4859-68, 1999).

C.   Use of IL-28A, IL-28B, and IL-29 in Immunocompromised Patients

IL-28 and IL-29 can be used as a monotherapy for acute and chronic

20   viral infections and for immunocompromised patients. Methods that enhance immunity can accelerate the recovery time in patients with unresolved infections. Immunotherapies can have an even greater impact on subsets of immunocompromised patients such as the very young or elderly as well as patients that suffer immunodeficiencies acquired through infection, or induced following medical

25   interventions such as chemotherapy or bone marrow ablation. Examples of the types of indications being treated via immune-modulation include; the use of IFN-α for chronic hepatitis (Perry CM, and Jarvis B, Drugs 61:2263-88, 2001), the use of IL-2 following HIV infection (Mitsuyasu R., J. Infect. Dis. 185 Suppl 2:S115-22, 2002; and Ross RW et al., Expert Opin. Biol. Ther. 1:413-24, 2001), and the use of either IFN-α (Faro A,

30   Springer Semin. Immunopathol.20:425-36, 1998) for treating Epstein Barr Virus infections following transplantation. Experiments performed in animal models indicate that IL-2 and GM-CSF may also be efficacious for treating EBV related diseases (Baiocchi RA et al., J Clin. Invest. 108:887-94, 2001).

35

In summary, IL-28, IL-29, or mutants thereof can be used:

(1) as a monotherapy for acute and chronic viral infections and for immunocompromised patients. Methods that enhance immunity can accelerate the recovery time in patients with unresolved infections.

(2) in combination with other antiviral agents such as ACYCLOVIR™, interferon plus RIBAVIRIN™.

(3) in combination with other immunotherapies including cytokines, immunoglobulin transfer, and various co-stimulatory molecules.

(4) to treat a mammal with a chronic or acute viral infection that has resulted liver inflammation, thereby reducing the viral infection and/or liver inflammation. In particular IL-28 and IL-29 will be used to treat a mammal with a viral infection selected from the group consisting of hepatitis A, hepatitis B, hepatitis C, and hepatitis D.

(5) as an antiviral agent in viral infections selected from the group consisting of respiratory syncytial virus, herpes virus, Epstein-Barr virus, influenza virus, adenovirus, parainfluenza virus, rhino virus, coxsackie virus, vaccinia virus, west nile virus, dengue virus, venezuelan equine encephalitis virus, pichinde virus and polio virus.

EXAMPLES

Example 1

Induction of IL-28A, IL-29, IL-28B by poly I:C and viral infection

Freshly isolated human peripheral blood mononuclear cells were grown in the presence of polyinosinic acid-polycytidylic acid (poly I:C; 100 µg/ml) (SIGMA; St. Louis, MO), encephalomyocarditis virus (EMCV) with an MOI of 0.1, or in medium alone. After a 15h incubation, total RNA was isolated from cells and treated with RNase-free DNase. 100 ng total RNA was used as template for one-step RT-PCR using the Superscript One-Step RT-PCR with Platinum Taq kit and gene-specific primers as suggested by the manufacturer (Invitrogen).

Low to undetectable amounts of human IL-28A, IL-28B, and IL-29, IFN-α and IFN-β RNA were seen in untreated cells. In contrast, the amount of IL-28A, IL-29, IL-28B RNA was increased by both poly I:C treatment and viral infection, as was also seen for the type I interferons. These experiments indicate that IL-28A, IL-29, IL-28B, like type I interferons, can be induced by double-stranded RNA or viral infection.

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Example 2
IL-28, IL-29 signaling activity compared to IFNα in HepG2 cells.

A.   Cell Transfections

5   HepG2 cells were transfected as follows: 700,000 HepG2 cells/well (6
well plates) were plated approximately 18h prior to transfection in 2 milliliters DMEM
+ 10% fetal bovine serum. Per well, 1 microgram pISRE-Luciferase DNA (Stratagene)
and 1 microgram pIRES2-EGFP DNA (Clontech,) were added to 6 microliters Fugene
6 reagent (Roche Biochemicals) in a total of 100 microliters DMEM. This transfection
10   mix was added 30 minutes later to the pre-plated HepG2 cells. Twenty-four hours later
the transfected cells were removed from the plate using trypsin-EDTA and replated at
approximately 25,000 cells/well in 96 well microtiter plates. Approximately 18 h prior
to ligand stimulation, media was changed to DMEM + 0.5%FBS.

15   B.   Signal Transduction Reporter Assays

              The signal transduction reporter assays were done as follows: Following
an 18h incubation at 37°C in DMEM + 0.5%FBS, transfected cells were stimulated
with 100 ng/ml IL-28A, IL-29, IL-28B, zcyto24, zcyto25 and huIFN-α2a ligands.
Following a 4-hour incubation at 37° degrees, the cells were lysed, and the relative light
20   units (RLU) were measured on a luminometer after addition of a luciferase substrate.
The results obtained are shown as the fold induction of the RLU of the experimental
samples over the medium alone control (RLU of experimental samples/RLU of medium
alone = fold induction).   Table 2 shows that IL-28A, IL-29, IL-28B, zcyto24 and
zcyto25 induce ISRE signaling in human HepG2 liver cells transfected with ISRE-
25   luciferase.

Table 2: Fold Induction of Cytokine-dependent ISRE Signaling in HepG2 Cells

Cytokine	Fold Inductn.
IL-28A	5.6
IL-29	4
IL-28B	5.8
Zcyto24	4.7
Zcyto25	3
HuIFN-a2a	5.8

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Example 3
IL-29 antiviral activity compared to IFNα in HepG2 cells.

5   An antiviral assay was adapted for EMCV (American Type Culture
Collection # VR-129B, Manassas, VA) with human cells (Familletti, P., et al., Methods
Enzym. 78: 387-394, 1981). Cells were plated with cytokines and incubated 24 hours
prior to challenge by EMCV at a multiplicity of infection of 0.1 to 1. The cells were
analyzed for viability with a dye-uptake bioassay 24 hours after infection (Berg, K., et
al., Apmis 98: 156-162, 1990). Target cells were given MTT and incubated at 37°C
10   for 2 hours. A solubiliser solution was added, incubated overnight at 37°C and the
optical density at 570 nm was determined. OD570 is directly proportional to antiviral
activity.

The results show the antiviral activity when IL-29 and IFN on were
tested with HepG2 cells: IL-29, IFN–β and IFN α-2a were added at varying
15   concentration to HepG2 cells prior to EMCV infection and dye-uptake assay. The
mean and standard deviation of the OD570 from triplicate wells is plotted. OD570 is
directly proportional to antiviral activity. For IL-29, the EC50 was 0.60 ng/ml; for IFN-
α2a, the EC50 was 0.57 ng/ml; and for IFN-β, the EC50 was 0.46ng/ml.

20   Example 4
IL-28RA mRNA expression in liver and lymphocyte subsets.

In order to further examine the mRNA distribution for IL-28RA, semi-
quantitative RT-PCR was performed using the SDS 7900HT system (Applied
25   Biosystems, CA).   One-step RT-PCR was performed using 100ng total RNA for each
sample and gene-specific primers. A standard curve was generated for each primer set
using Bjab RNA and all sample values were normalized to HPRT. The normalized
results are summarized in Tables 2-4. The normalized values for IFNAR2 and CRF2-4
are also shown.

30   Table 3: B and T cells express significant levels of IL-28RA mRNA.
Low levels are seen in dendritic cells and most monocytes.

Table 3

Cell/Tissue	IL-28RA	IFNAR2	CRF2-4
Dendritic Cells unstim	.04	5.9	9.8
Dendritic Cells +IFNg	.07	3.6	4.3
Dendritic Cells	.16	7.85	3.9
CD14+ stim'd with LPS/IFNg	.13	12	27
CD14+ monocytes resting	.12	11	15.4
Hu CD14+ Unact.	4.2	TBD	TBD

Hu CD14+ 1 ug/ml LPS act.	2.3	TBD	TBD
H. Inflamed tonsil	3	12.4	9.5
H. B-cells+PMA/Iono 4 & 24 hrs	3.6	1.3	1.4
Hu CD19+ resting	6.2	TBD	TBD
Hu CD19+ 4 hr. PMA/Iono	10.6	TBD	TBD
Hu CD19+ 24 hr Act. PMA/Iono	3.7	TBD	TBD
IgD+ B-cells	6.47	13.15	6.42
IgM+ B-cells	9.06	15.4	2.18
IgD- B-cells	5.66	2.86	6.76
NKCells + PMA/Iono	0	6.7	2.9
Hu CD3+ Unactivated	2.1	TBD	TBD
CD4+ resting	.9	8.5	29.1
CD4+ Unstim 18 hrs	1.6	8.4	13.2
CD4+ +Poly I/C	2.2	4.5	5.1
CD4+ + PMA/Iono	.3	1.8	.9
CD3 neg resting	1.6	7.3	46
CD3 neg unstim 18 hrs	2.4	13.2	16.8
CD3 neg+Poly I/C 18 hrs	5.7	7	30.2
CD3 neg+LPS 18 hrs	3.1	11.9	28.2
CD8+ unstim 18 hrs	1.8	4.9	13.1
CD8+ stim'd with PMA/Ion 18 hrs	.3	.6	1.1

As shown in Table 4, normal liver tissue and liver derived cell lines display substantial levels of IL-28RA and CRF2-4 mRNA.

Table 4

Cell/Tissue	IL-28RA	IFNAR2	CRF2-4
HepG2	1.6	3.56	2.1
HepG2 UGAR 5/10/02	1.1	1.2	2.7
HepG2, CGAT HKES081501C	4.3	2.1	6
HuH7 5/10/02	1.63	16	2
HuH7 hepatoma – CGAT	4.2	7.2	3.1
Liver, normal – CGAT #HXYZ020801K	11.7	3.2	8.4
Liver, NAT - Normal adjacent tissue	4.5	4.9	7.7
Liver, NAT - Normal adjacent tissue	2.2	6.3	10.4
Hep SMVC hep vein	0	1.4	6.5
Hep SMCA hep. Artery	0	2.1	7.5
Hep. Fibro	0	2.9	6.2
Hep. Ca.	3.8	2.9	5.8
Adenoca liver	8.3	4.2	10.5
SK-Hep-1 adenoca. Liver	.1	1.3	2.5
AsPC-1 Hu. Pancreatic adenocarc.	.7	.8	1.3
Hu. Hep. Stellate cells	.025	4.4	9.7

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As shown in Table 5, primary airway epithelial cells contain abundant levels of IL-28RA and CRF2-4.

Table 5

Cell/Tissue	IL-28RA	IFNAR2	CRF2-4
U87MG - glioma	0	.66	.99
NHBE unstim	1.9	1.7	8.8
NHBE + TNF-alpha	2.2	5.7	4.6
NHBE + poly I/C	1.8	nd	nd
Small Airway Epithelial Cells	3.9	3.3	27.8
NHLF - Normal human lung fibroblasts	0	nd	nd

As shown in Table 6, IL-28RA is present in normal and diseased liver specimens, with increased expression in tissue from Hepatitis C and Hepatitis B infected specimens.

Table 6

Cell/Tissue	IL-28RA	CRF2-4	IFNAR2
Liver with Coagulation Necrosis	8.87	15.12	1.72
Liver with Autoimmune Hepatitis	6.46	8.90	3.07
Neonatal Hepatitis	6.29	12.46	6.16
Endstage Liver disease	4.79	17.05	10.58
Fulminant Liver Failure	1.90	14.20	7.69
Fulminant Liver failure	2.52	11.25	8.84
Cirrhosis, primary biliary	4.64	12.03	3.62
Cirrhosis Alcoholic (Laennec's)	4.17	8.30	4.14
Cirrhosis, Cryptogenic	4.84	7.13	5.06
Hepatitis C+, with cirrhosis	3.64	7.99	6.62
Hepatitis C+	6.32	11.29	7.43
Fulminant hepatitis secondary to Hep A	8.94	21.63	8.48
Hepatitis C+	7.69	15.88	8.05
Hepatitis B+	1.61	12.79	6.93
Normal Liver	8.76	5.42	3.78
Normal Liver	1.46	4.13	4.83
Liver NAT	3.61	5.43	6.42
Liver NAT	1.97	10.37	6.31
Hu Fetal Liver	1.07	4.87	3.98
Hepatocellular Carcinoma	3.58	3.80	3.22
Adenocarcinoma Liver	8.30	10.48	4.17
hep. SMVC, hep. Vein	0.00	6.46	1.45
Hep SMCA hep. Artery	0.00	7.55	2.10

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Hep. Fibroblast	0.00	6.20	2.94
HuH7 hepatoma	4.20	3.05	7.24
HepG2 Hepatocellular carcinoma	3.40	5.98	2.11
SK-Hep-1 adenocar. Liver	0.03	2.53	1.30
HepG2 Unstim	2.06	2.98	2.28
HepG2+zcyto21	2.28	3.01	2.53
HepG2+IFNα	2.61	3.05	3.00
Normal Female Liver - degraded	1.38	6.45	4.57
Normal Liver - degraded	1.93	4.99	6.25
Normal Liver - degraded	2.41	2.32	2.75
Disease Liver - degraded	2.33	3.00	6.04
Primary Hepatocytes from Clonetics	9.13	7.97	13.30

As shown in Tables 7-11, IL-28RA is detectable in normal B cells, B lymphoma cell lines, T cells, T lymphoma cell lines (Jurkat), normal and transformed lymphocytes (B cells and T cells) and normal human monocytes.

Table 7

	HPRT Mean	IL-28RA Mean	IL-28RA norm	IFNAR2	IFNR2 norm	CRF2-4	CRF2-4 Norm
CD14+ 24hr unstim #A38	13.1	68.9	5.2	92.3	7.0	199.8	15.2
CD14+ 24 hr stim #A38	6.9	7.6	1.1	219.5	31.8	276.6	40.1
CD14+ 24 hr unstim #A112	17.5	40.6	2.3	163.8	9.4	239.7	13.7
CD14+ 24 hr stim #A112	11.8	6.4	0.5	264.6	22.4	266.9	22.6
CD14+ rest #X	32.0	164.2	5.1	1279.7	39.9	699.9	21.8
CD14+ +LPS #X	21.4	40.8	1.9	338.2	15.8	518.0	24.2
CD14+ 24 hr unstim #A39	26.3	86.8	3.3	297.4	11.3	480.6	18.3
CD14+ 24 hr stim #A39	16.6	12.5	0.8	210.0	12.7	406.4	24.5
HL60 Resting	161.2	0.2	0.0	214.2	1.3	264.0	1.6
HL60+PMA	23.6	2.8	0.1	372.5	15.8	397.5	16.8
U937 Resting	246.7	0.0	0.0	449.4	1.8	362.5	1.5
U937+PMA	222.7	0.0	0.0	379.2	1.7	475.9	2.1
Jurkat Resting	241.7	103.0	0.4	327.7	1.4	36.1	0.1
Jurkat Activated	130.7	143.2	1.1				
Colo205	88.8	43.5	0.5				
HT-29	26.5	30.5	1.2				

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Table 8

	HPRT SD	IL-28RA SD
Mono 24hr unstim #A38	0.6	2.4
Mono 24 hr stim #A38	0.7	0.2
Mono 24 hr unstim #A112	2.0	0.7
Mono 24 hr stim #A112	0.3	0.1
Mono rest #X	5.7	2.2
Mono+LPS #X	0.5	1.0
Mono 24 hr unstim #A39	0.7	0.8
Mono 24 hr stim #A39	0.1	0.7
HL60 Resting	19.7	0.1
HL60+PMA	0.7	0.4
U937 Resting	7.4	0.0
U937+PMA	7.1	0.0
Jurkat Resting	3.7	1.1
Jurkat Activated	2.4	1.8
Colo205	1.9	0.7
HT-29	2.3	1.7

Table 9

	Mean Hprt	Mean IFNAR2	Mean IL-28RA	Mean CRF
CD3+/CD4+ 0	10.1	85.9	9.0	294.6
CD4/CD3+ Unstim 18 hrs	12.9	108.7	20.3	170.4
CD4+/CD3+ +Poly I/C 18 hrs	24.1	108.5	52.1	121.8
CD4+/CD3+ + PMA/Iono 18 hrs	47.8	83.7	16.5	40.8
CD3 neg 0	15.4	111.7	24.8	706.1
CD3 neg unstim 18 hrs	15.7	206.6	37.5	263.0
CD3 neg +Poly I/C 18 hrs	9.6	67.0	54.7	289.5
CD3 neg +LPS 18 hrs	14.5	173.2	44.6	409.3
CD8+ Unstim. 18 hrs	6.1	29.7	11.1	79.9
CD8+ + PMA/Iono 18 hrs	78.4	47.6	26.1	85.5
12.8.1 - NHBE Unstim	47.4	81.1	76.5	415.6
12.8.2 - NHBE+TNF-alpha	42.3	238.8	127.7	193.9
SAEC	15.3	49.9	63.6	426.0

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Table 10

	IL-28RA Norm	CRF Norm	IFNAR2 Norm	IL-28RA SD	CRF SD	IFNAR2 SD
CD3+/CD4+ 0	0.9	29.1	8.5	0.1	1.6	0.4
CD4/CD3+ Unstim 18 hrs	1.6	13.2	8.4	0.2	1.6	1.4
CD4+/CD3+ +Poly I/C 18 hrs	2.2	5.1	4.5	0.1	0.3	0.5
CD4+/CD3+ + PMA/Iono 18 hrs	0.3	0.9	1.8	0.0	0.1	0.3
CD3 neg 0	1.6	46.0	7.3	0.2	4.7	1.3
CD3 neg unstim 18 hrs	2.4	16.8	13.2	0.4	2.7	2.3
CD3 neg +Poly I/C 18 hrs	5.7	30.2	7.0	0.3	1.7	0.8
CD3 neg +LPS 18 hrs	3.1	28.2	11.9	0.4	5.4	2.9
CD8+ Unstim. 18 hrs	1.8	13.1	4.9	0.1	1.1	0.3
CD8+ + PMA/Iono 18 hrs	0.3	1.1	0.6	0.0	0.1	0.0
12.8.1 - NHBE Unstim	1.6	8.8	1.7	0.1	0.4	0.1
12.8.2 - NHBE+TNF-alpha	3.0	4.6	5.7	0.1	0.1	0.1
SAEC	4.1	27.8	3.3	0.2	1.1	0.3

Table 11

	SD Hprt	SD IFNAR2	SD IL-28RA	SD CRF
CD3+/CD4+ 0	0.3	3.5	0.6	12.8
CD4/CD3+ Unstim 18 hrs	1.4	13.7	1.1	8.5
CD4+/CD3+ +Poly I/C 18 hrs	1.3	9.8	1.6	3.4
CD4+/CD3+ + PMA/Iono 18 hrs	4.0	10.3	0.7	3.7
CD3 neg 0	1.4	16.6	1.6	28.6
CD3 neg unstim 18 hrs	2.4	16.2	2.7	12.6
CD3 neg +Poly I/C 18 hrs	0.5	7.0	1.0	8.3
CD3 neg +LPS 18 hrs	1.0	39.8	5.6	73.6
CD8+ Unstim. 18 hrs	0.2	1.6	0.5	6.1
CD8+ + PMA/Iono 18 hrs	1.3	1.7	0.2	8.1
12.8.1 - NHBE Unstim	2.4	5.6	2.7	2.8
12.8.2 - NHBE+TNF-alpha	0.5	3.4	3.5	3.4
SAEC	0.5	4.8	1.8	9.9

Example 5

Mouse IL-28 Does Not Effect Daudi Cell Proliferation

Human Daudi cells were suspended in RPMI + 10%FBS at 50,000 cells/milliliter and 5000 cells were plated per well in a 96 well plate. IL-29-CEE (IL-29 conjugated with glu tag), IFN-γ or IFN-α2a was added in 2-fold serial dilutions to each well. IL-29-CEE was used at a concentration range of from 1000 ng/ml to 0.5 ng/ml. IFN-γ was used at a concentration range from 125 ng/ml to 0.06 ng/ml. IFN-α2a was

used at a concentration range of from 62 ng/ml to 0.03 ng/ml. Cells were incubated for 72 h at 37°C. After 72 h. Alamar Blue (Accumed, Chicago, IL) was added at 20 microliters/well. Plates were further incubated at 37°C., 5% CO, for 24 hours. Plates were read on the Fmax™ plate reader (Molecular Devices, Sunnyvale, CA) using the

5   SoftMax™ Pro program, at wavelengths 544 (Excitation) and 590 (Emission). Alamar Blue gives a fluourometric readout based on the metabolic activity of cells, and is thus a direct measurement of cell proliferation in comparison to a negative control. The results indicate that IL-29-CEE, in contrast to IFN-α2a, has no significant effect on proliferation of Daudi cells.

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Example 6

Mouse IL-28 Does Not Have Antiproliferative Effect on Mouse B cells

        Mouse B cells were isolated from 2 Balb/C spleens (7 months old) by depleting CD43+ cells using MACS magnetic beads. Purified B cells were cultured in

15   vitro with LPS, anti-IgM or anti-CD40 monoclonal antibodies. Mouse IL-28 or mouse IFNα was added to the cultures and ^{3}H-thymidine was added at 48 hrs. and ^{3}H-thymidine incorporation was measured after 72 hrs. culture.

        IFNα at 10 ng/ml inhibited ^{3}H-thymidine incorporation by mouse B cells stimulated with either LPS or anti-IgM. However mouse IL-28 did not inhibit ^{3}H-

20   thymidine incorporation at any concentration tested including 1000 ng/ml. In contrast, both mIFNα and mouse IL-28 increased ^{3}H thymidine incorporation by mouse B cells stimulated with anti-CD40 MAb.

        These data demonstrate that mouse IL-28 unlike IFNa displays no antiproliferative activity even at high concentrations. In addition, zcyto24 enhances

25   proliferation in the presence of anti-CD40 MAbs. The results illustrate that mouse IL-28 differs from IFNα in that mouse IL-28 does not display antiproliferative activity on mouse B cells, even at high concentrations. In addition, mouse IL-28 enhances proliferation in the presence of anti-CD40 monoclonal antibodies.

30   Example 7

Bone marrow expansion assay

        Fresh human marrow mononuclear cells (Poietic Technologies, Gaithersburg, Md.) were adhered to plastic for 2 hrs in αMEM, 10% FBS, 50 micromolar β–mercaptoethanol, 2 ng/ml FLT3L at 37ºC. Non adherent cells were

35   then plated at 25,000 to 45,000 cells/well (96 well tissue culture plates) in αMEM, 10% FBS, 50 micromolar β–mercaptoethanol, 2 ng/ml FLT3L in the presence or absence of

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1000 ng/ml IL-29-CEE, 100 ng/ml IL-29-CEE, 10 ng/ml IL-29-CEE, 100 ng/ml IFN-α2a, 10 ng/ml IFN- α2a or 1 ng/ml IFN- α2a. These cells were incubated with a variety of cytokines to test for expansion or differentiation of hematopoietic cells from the marrow (20 ng/ml IL-2, 2 ng/ml IL-3, 20 ng/ml IL-4, 20 ng/ml IL-5, 20 ng/ml IL-7, 20 ng/ml IL-10, 20 ng/ml IL-12, 20 ng/ml IL-15, 10 ng/ml IL-21 or no added cytokine). After 8 to 12 days Alamar Blue (Accumed, Chicago, Ill.) was added at 20 microliters/well. Plates were further incubated at 37 °C, 5% CO, for 24 hours. Plates were read on the Fmax™ plate reader (Molecular Devices Sunnyvale, Calif.) using the SoftMax™ Pro program, at wavelengths 544 (Excitation) and 590 (Emission). Alamar Blue gives a fluourometric readout based on the metabolic activity of cells, and is thus a direct measurement of cell proliferation in comparison to a negative control.

IFN- α2a caused a significant inhibition of bone marrow expansion under all conditions' tested. In contrast, IL-29 had no significant effect on expansion of bone marrow cells in the presence of IL-3, IL-4, IL-5, IL-7, IL-10, IL-12, IL-21 or no added cytokine. A small inhibition of bone marrow cell expansion was seen in the presence of IL-2 or IL-15.

Example 8
Inhibition of IL-28 and IL-29 signaling with soluble receptor (zcytoR19/CRF2-4).

A.   Signal Transduction Reporter Assay

A signal transduction reporter assay can be used to show the inhibitor properties of zcytor19-Fc4 homodimeric and zcytor19-Fc/CRF2-4-Fc heterodimeric soluble receptors on zcyto20, zcyto21 and zcyto24 signaling. Human embryonal kidney (HEK) cells overexpressing the zcytor19 receptor are transfected with a reporter plasmid containing an interferon-stimulated response element (ISRE) driving transcription of a luciferase reporter gene. Luciferase activity following stimulation of transfected cells with ligands (including zcyto20 (SEQ ID NO:18), zcyto21 (SEQ ID NO:20), zcyto24 (SEQ ID NO:8)) reflects the interaction of the ligand with soluble receptor.

B.   Cell Transfections

293 HEK cells overexpressing zcytor19 were transfected as follows: 700,000 293 cells/well (6 well plates) were plated approximately 18h prior to transfection in 2 milliliters DMEM + 10% fetal bovine serum. Per well, 1 microgram pISRE-Luciferase DNA (Stratagene) and 1 microgram pIRES2-EGFP DNA (Clontech,)

were added to 6 microliters Fugene 6 reagent (Roche Biochemicals) in a total of 100 microliters DMEM. This transfection mix was added 30 minutes later to the pre-plated 293 cells. Twenty-four hours later the transfected cells were removed from the plate using trypsin-EDTA and replated at approximately 25,000 cells/well in 96 well

5   microtiter plates. Approximately 18 h prior to ligand stimulation, media was changed to DMEM + 0.5%FBS.

C.   Signal Transduction Reporter Assays

            The signal transduction reporter assays were done as follows: Following
10 an 18h incubation at 37°C in DMEM + 0.5%FBS, transfected cells were stimulated with 10 ng/ml zcyto20, zcyto21 or zcyto24 and 10 micrograms/ml of the following soluble receptors; human zcytor19-Fc homodimer, human zcytor19-Fc/human CRF2-4-Fc heterodimer, human CRF2-4-Fc homodimer, murine zcytor19-Ig homodimer. Following a 4-hour incubation at 37°C, the cells were lysed, and the relative light units
15 (RLU) were measured on a luminometer after addition of a luciferase substrate. The results obtained are shown as the percent inhibition of ligand-induced signaling in the presence of soluble receptor relative to the signaling in the presence of PBS alone. Table 11 shows that the human zcytor19-Fc/human CRF2-4 heterodimeric soluble receptor is able to inhibit zcyto20, zcyto21 and zcyto24-induced signaling between 16
20 and 45% of control. The human zcytor19-Fc homodimeric soluble receptor is also able to inhibit zcyto21-induced signaling by 45%. No significant effects were seen with huCRF2-4-Fc or muzcytor19-Ig homodimeric soluble receptors.

Table 12: Percent Inhibition of Ligand-induced Interferon Stimulated
25 Response Element (ISRE) Signaling by Soluble Receptors

Ligand	Huzcytor19-Fc/huCRF2-4-Fc	Huzcytor19-Fc	HuCRF2-4-Fc	Muzcytor19-Ig
Zcyto20	16%	92%	80%	91%
Zcyto21	16%	45%	79%	103%
Zcyto24	47%	90%	82%	89%

Example 9
IL-28 and IL-29 inhibit HIV replication in fresh human PBMCs

            Human immunodeficiency virus (HIV) is a pathogenic retrovirus that
30 infects cells of the immune system. CD4 T cells and monocytes are the primary infected

cell types. To test the ability of IL-28 and IL-29 to inhibit HIV replication *in vitro*, PBMCs from normal donors were infected with the HIV virus in the presence of IL-28, IL-29 and MetIL-29C172S-PEG.

Fresh human peripheral blood mononuclear cells (PBMCs) were isolated

5   from whole blood obtained from screened donors who were seronegative for HIV and HBV. Peripheral blood cells were pelleted/washed 2-3 times by low speed centrifugation and resuspended in PBS to remove contaminating platelets. The washed blood cells were diluted 1:1 with Dulbecco's phosphate buffered saline (D-PBS) and layered over 14 mL of Lymphocyte Separation Medium ((LSM; cellgro™ by

10   Mediatech, Inc. Herndon, VA); density 1.078 +/-0.002 g/ml) in a 50 mL centrifuge tube and centrifuged for 30 minutes at 600 x G. Banded PBMCs were gently aspirated from the resulting interface and subsequently washed 2X in PBS by low speed centrifugation. After the final wash, cells were counted by trypan blue exclusion and resuspended at 1 x 10^7 cells/mL in RPMI 1640 supplemented with 15% Fetal Bovine Serum (FBS), 2

15   mM L-glutamine, 4 μg/mL PHA-P. The cells were allowed to incubate for 48-72 hours at 37°C. After incubation, PBMCs were centrifuged and resuspended in RPMI 1640 with 15% FBS, 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, 10 μg/mL gentamycin, and 20 U/mL recombinant human IL-2. PBMCs were maintained in the medium at a concentration of 1-2 x 10^6 cells/mL with biweekly medium changes

20   until used in the assay protocol. Monocytes were depleted from the culture as the result of adherence to the tissue culture flask.

For the standard PBMC assay, PHA-P stimulated cells from at least two normal donors were pooled, diluted in fresh medium to a final concentration of 1 x 10^6 cells/mL, and plated in the interior wells of a 96 well round bottom microplate at 50

25   μL/well (5 x 10^4 cells/well). Test dilutions were prepared at a 2X concentration in microtiter tubes and 100 μL of each concentration was placed in appropriate wells in a standard format. IL-28, IL-29 and MetIL-29C172S-PEG were added at concentrations from 0-10 μg/ml, usually in 1/2 log dilutions. 50 μL of a predetermined dilution of virus stock was placed in each test well (final MOI of 0.1). Wells with only cells and virus

30   added were used for virus control. Separate plates were prepared identically without virus for drug cytotoxicity studies using an MTS assay system. The PBMC cultures were maintained for seven days following infection, at which time cell-free supernatant samples were collected and assayed for reverse transcriptase activity and p24 antigen levels.

35   A decrease in reverse transcriptase activity or p24 antigen levels with IL-28, IL-29 and MetIL-29C172S-PEG would be indicators of antiviral activity. Result

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would demonstrate that IL-28 and IL-29 may have therapeutic value in treating HIV and AIDS.

Example 10

5   IL-28 and IL-29 inhibit GBV-B replication in marmoset liver cells

HCV is a member of the *Flaviviridae* family of RNA viruses. HCV does not replicate well in either *ex-vivo* or *in vitro* cultures and therefore, there are no satisfactory systems to test the anti-HCV activity of molecules *in vitro*. GB virus B (GBV-B) is an attractive surrogate model for use in the development of anti-HCV

10   antiviral agents since it has a relatively high level of sequence identity with HCV and is a hepatotropic virus. To date, the virus can only be grown in the primary hepatocytes of certain non-human primates. This is accomplished by either isolating hepatocytes *in vitro* and infecting them with GBV-B, or by isolating hepatocytes from GBV-B infected marmosets and directly using them with antiviral compounds.

15   The effects of IL-28, IL-29 and MetIL-29C172S-PEG are assayed on GBV-B extracellular RNA production by TaqMan RT-PCR and on cytotoxicity using CellTiter96® reagent (Promega, Madison, WI) at six half-log dilutions IL-28, IL-29 or MetIL-29C172S-PEG polypeptide in triplicate. Untreated cultures serve as the cell and virus controls. Both RIBAVIRIN® (200 μg/ml at the highest test concentration) and

20   IFN-α (5000 IU/ml at the highest test) are included as positive control compounds. Primary hepatocyte cultures are isolated and plated out on collagen-coated plates. The next day the cultures are treated with the test samples (IL-28, IL-29, MetIL-29C172S-PEG, IFNα, or RIBAVIRIN®) for 24hr before being exposed to GBV-B virions or treated directly with test samples when using *in vivo* infected hepatocytes. Test samples

25   and media are added the next day, and replaced three days later. Three to four days later (at day 6-7 post test sample addition) the supernatant is collected and the cell numbers quantitated with CellTiter96®. Viral RNA is extracted from the supernatant and quantified with triplicate replicates in a quantitative TaqMan RT-PCR assay using an *in vitro* transcribed RNA containing the RT-PCR target as a standard. The average

30   of replicate samples is computed. Inhibition of virus production is assessed by plotting the average RNA and cell number values of the triplicate samples relative to the untreated virus and cell controls. The inhibitory concentration of drug resulting in 50% inhibition of GBV-B RNA production (IC50) and the toxic concentration resulting in destruction of 50% of cell numbers relative to control values (TC50) are calculated by

35   interpolation from graphs created with the data.

Inhibition of the GBV-B RNA production by IL-28 and 29 is an indication of the antiviral properties of IL-28 and IL-29 on this Hepatitis C-like virus on hepatocytes, the primary organ of infection of Hepatitis C, and positive results suggest that IL-28 or IL-29 may be useful in treating HCV infections in humans.

Example 11

IL-28, IL-29 and MetIL-29C172S-PEG inhibit HBV replication in WT10 cells

Chronic hepatitis B (HBV) is one of the most common and severe viral infections of humans belonging to the *Hepadnaviridae* family of viruses. To test the antiviral activities of IL-28 and IL-29 against HBV, IL-28, IL-29 and MetIL-29C172S-PEG were tested against HBV in an *in vitro* infection system using a variant of the human liver line HepG2. IL-28, IL-29 and MetIL-29C172S-PEG inhibited viral replication in this system, suggesting therapeutic value in treating HBV in humans.

WT10 cells are a derivative of the human liver cell line HepG2 2.2.15. WT10 cells are stably transfected with the HBV genome, enabling stable expression of HBV transcripts in the cell line (Fu and Cheng, Antimicrobial Agents Chemother. 44(12):3402-3407, 2000). In the WT10 assay the drug in question and a 3TC control will be assayed at five concentrations each, diluted in a half-log series. The endpoints are TaqMan PCR for extracellular HBV DNA (IC50) and cell numbers using CellTiter96 reagent (TC50). The assay is similar to that described by Korba et al. Antiviral Res. 15(3):217-228, 1991 and Korba et al., Antiviral Res. 19(1):55-70, 1992. Briefly, WT10 cells are plated in 96-well microtiter plates. After 16-24 hours the confluent monolayer of HepG2-2.2.15 cells is washed and the medium is replaced with complete medium containing varying concentrations of a test samples in triplicate. 3TC is used as the positive control, while media alone is added to cells as a negative control (virus control, VC). Three days later the culture medium is replaced with fresh medium containing the appropriately diluted test samples. Six days following the initial addition of the test compound, the cell culture supernatant is collected, treated with pronase and DNAse, and used in a real-time quantitative TaqMan PCR assay. The PCR-amplified HBV DNA is detected in real-time by monitoring increases in fluorescence signals that result from the exonucleolytic degradation of a quenched fluorescent probe molecule that hybridizes to the amplified HBV DNA. For each PCR amplification, a standard curve is simultaneously generated using dilutions of purified HBV DNA. Antiviral activity is calculated from the reduction in HBV DNA levels (IC$_{50}$). A dye uptake assay is then employed to measure cell viability which is used to calculate toxicity (TC$_{50}$). The therapeutic index (TI) is calculated as TC$_{50}$/IC$_{50}$.

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IL-28, IL-29 and MetIL-29C172S-PEG inhibited HepB viral replication in WT10 cells with an IC50 < 0.032ug/ml. This demonstrates antiviral activity of IL-28 and IL-29 against HBV grown in liver cell lines, providing evidence of therapeutic value for treating HBV in human patients.

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Example 12

IL-28, IL-29 and MetIL-29C172S-PEG inhibit BVDV replication in bovine kidney cells

HCV is a member of the *Flaviviridae* family of RNA viruses. Other viruses belonging to this family are the bovine viral diarrhea virus (BVDV) and yellow
10   fever virus (YFV). HCV does not replicate well in either *ex vivo* or *in vitro* cultures and therefore there are no systems to test anti-HCV activity in vitro. The BVDV and YFV assays are used as surrogate viruses for HCV to test the antiviral activities against the *Flavivirida* family of viruses.

The antiviral effects of IL-28, IL-29 and MetIL-29C172S-PEG were
15   assessed in inhibition of cytopathic effect assays (CPE). The assay measured cell death using Madin-Darby bovine kidney cells (MDBK) after infection with cytopathic BVDV virus and the inhibition of cell death by addition of IL-28, IL-29 and MetIL-29C172S-PEG. The MDBK cells were propagated in Dulbecco's modified essential medium (DMEM) containing phenol red with 10% horse serum, 1% glutamine and 1%
20   penicillin-streptomycin. CPE inhibition assays were performed in DMEM without phenol red with 2% FBS, 1% glutamine and 1% Pen-Strep. On the day preceding the assays, cells were trypsinized (1% trypsin-EDTA), washed, counted and plated out at 10^4 cells/well in a 96-well flat-bottom BioCoat® plates (Fisher Scientific, Pittsburgh, PA) in a volume of 100 µl/well. The next day, the medium was removed and a pre-
25   titered aliquot of virus was added to the cells. The amount of virus was the maximum dilution that would yield complete cell killing (>80%) at the time of maximal CPE development (day 7 for BVDV). Cell viability was determined using a CellTiter96® reagent (Promega) according to the manufacturer's protocol, using a Vmax plate reader (Molecular Devices, Sunnyvale, CA). Test samples were tested at six concentrations
30   each, diluted in assay medium in a half-log series. IFNα and RIBAVIRIN® were used as positive controls. Test sample were added at the time of viral infection. The average background and sample color-corrected data for percent CPE reduction and percent cell viability at each concentration were determined relative to controls and the IC_{50} calculated relative to the TC_{50}.

35   IL-28, IL-29 and MetIL-29C172S-PEG inhibited cell death induced by BVDV in MDBK bovine kidney cells. IL-28 inhibited cell death with an IC_{50} of 0.02

µg/ml, IL-29 inhibited cell death with an IC_{50} of 0.19 µg/ml, and MetIL-29C172S-PEG inhibited cell death with an IC_{50} of 0.45 µg/ml. This demonstrated that IL-28 and IL-29 have antiviral activity against the *Flavivirida* family of viruses..

5   Example 13

Induction of Interferon Stimulated Genes by IL-28 and IL-29

A.   Human Peripheral Blood Mononuclear Cells

Freshly isolated human peripheral blood mononuclear cells were grown

10   in the presence of IL-29 (20 ng/mL), IFNα2a (2 ng/ml) (PBL Biomedical Labs, Piscataway, NJ), or in medium alone. Cells were incubated for 6, 24, 48, or 72 hours, and then total RNA was isolated and treated with RNase-free DNase. 100 ng total RNA was used as a template for One-Step Semi-Quantitative RT-PCR® using Taqman One-Step RT-PCR Master Mix® Reagents and gene specific primers as suggested by

15   the manufacturer. (Applied Biosystems, Branchburg, NJ) Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each time-point. Table 13 shows that IL-29 induces Interferon Stimulated Gene Expression in human peripheral blood mononuclear cells at all time-points tested.

Table 13

	MxA Fold induction	Pkr Fold Induction	OAS Fold Induction
6 hr IL29	3.1	2.1	2.5
6 hr IFNα2a	17.2	9.6	16.2
24 hr IL29	19.2	5.0	8.8
24 hr IFNα2a	57.2	9.4	22.3
48 hr IL29	7.9	3.5	3.3
48hr IFNα2a	18.1	5.0	17.3
72 hr IL29	9.4	3.7	9.6
72 hr IFNα2a	29.9	6.4	47.3

20

B.   Activated Human T Cells

Human T cells were isolated by negative selection from freshly harvested peripheral blood mononuclear cells using the Pan T-cell Isolation® kit

25   according to manufacturer's instructions (Miltenyi, Auburn, CA). T cells were then activated and expanded for 5 days with plate-bound anti-CD3, soluble anti-CD28

(0.5ug/ml), (Pharmingen, San Diego, CA) and Interleukin 2 (IL-2; 100 U/ml) (R&D Systems, Minneapolis, MN), washed and then expanded for a further 5 days with IL-2. Following activation and expansion, cells were stimulated with IL-28A (20 ng/ml), IL-29 (20 ng/ml), or medium alone for 3, 6, or 18 hours. Total RNA was isolated and

5   treated with RNase-Free DNase. One-Step Semi-Quantitative RT-PCR® was performed as described in the example above.   Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each time-point. Table 14 shows that IL-28 and IL-29 induce Interferon Stimulated Gene expression in activated human T cells at all time-points tested.

10

Table 14

	MxA Fold Induction	Pkr Fold Induction	OAS Fold Induction
Donor #1 3 hr IL28	5.2	2.8	4.8
Donor #1 3 hr IL29	5.0	3.5	6.0
Donor #1 6 hr IL28	5.5	2.2	3.0
Donor #1 6 hr IL29	6.4	2.2	3.7
Donor #1 18 hr IL28	4.6	4.8	4.0
Donor #1 18 hr IL29	5.0	3.8	4.1
Donor #2 3 hr IL28	5.7	2.2	3.5
Donor #2 3 hr IL29	6.2	2.8	4.7
Donor #2 6 hr IL28	7.3	1.9	4.4
Donor #2 6 hr IL29	8.7	2.6	4.9
Donor #2 18 hr IL28	4.7	2.3	3.6
Donor #2 18 hr IL29	4.9	2.1	3.8

C.   Primary Human Hepatocytes

Freshly isolated human hepatocytes from two separate donors (Cambrex, Baltimore, MD and CellzDirect, Tucson, AZ) were stimulated with IL-28A (50 ng/ml),

15   IL-29 (50 ng/ml), IFNα2a (50 ng/ml), or medium alone for 24 hours. Following stimulation, total RNA was isolated and treated with RNase-Free DNase. One-step semi-quantitative RT-PCR was performed as described previously in the example above. Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each time-point.   Table 15 shows that IL-28 and IL-29

20   induce Interferon Stimulated Gene expression in primary human hepatocytes following 24-hour stimulation.

39

Table 15

	MxA Fold Induction	Pkr Fold Induction	OAS Fold Induction
Donor #1 IL28	31.4	6.4	30.4
Donor #1 IL29	31.8	5.2	27.8
Donor #1 IFN-α2a	63.4	8.2	66.7
Donor #2 IL28	41.7	4.2	24.3
Donor #2 IL29	44.8	5.2	25.2
Donor #2 IFN-α2a	53.2	4.8	38.3

D.   HepG2 and HuH7: Human Liver Hepatoma Cell Lines

5   HepG2 and HuH7 cells (ATCC NOS. 8065, Manassas, VA) were stimulated with IL-28A (10 ng/ml), IL-29 (10 ng/ml), IFNα2a (10 ng/ml), IFNB (1 ng/ml) (PBL Biomedical, Piscataway, NJ), or medium alone for 24 or 48 hours. In a separate culture, HepG2 cells were stimulated as described above with 20 ng/ml of MetIL-29C172S-PEG or MetIL-29-PEG. Total RNA was isolated and treated with RNase-Free DNase. 100 ng Total RNA was used as a template for one-step semi-
10   quantitative RT-PCR as described previously. Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each time-point. Table 16 shows that IL-28 and IL-29 induce ISG expression in HepG2 and HuH7 liver hepatoma cell lines after 24 and 48 hours.

Table 16

	MxA Fold Induction	Pkr Fold Induction	OAS Fold Induction
HepG2 24 hr IL28	12.4	0.7	3.3
HepG2 24 hr IL29	36.6	2.2	6.4
HepG2 24 hr IFNα2a	12.2	1.9	3.2
HepG2 24 hr IFNβ	93.6	3.9	19.0
HepG2 48hr IL28	2.7	0.9	1.1
HepG2 48hr IL29	27.2	2.1	5.3
HepG2 48 hr IFNα2a	2.5	0.9	1.2
HepG2 48hr IFNβ	15.9	1.8	3.3
HuH7 24 hr IL28	132.5	5.4	52.6
HuH7 24 hr IL29	220.2	7.0	116.6
HuH7 24 hr IFNα2a	157.0	5.7	67.0
HuH7 24 hr IFNβ	279.8	5.6	151.8
HuH7 48hr IL28	25.6	3.4	10.3
HuH7 48hr IL29	143.5	7.4	60.3
HuH7 48 hr IFNα2a	91.3	5.8	32.3
HuH7 48hr IFNβ	65.0	4.2	35.7

Table 17

	MxA Fold Induction	OAS Fold Induction	Pkr Fold Induction
MetIL-29-PEG	36.7	6.9	2.2
MetIL-29C172S-PEG	46.1	8.9	2.8

Data shown is for 20 ng/ml metIL-29-PEG and metIL-29C172S-PEG versions of IL-29
after culture for 24 hours.

Data shown is normalized to HPRT and shown as fold induction over
unstimulated cells.

Example 14

Antiviral Activity of IL-28 and IL-29 in HCV Replicon System

The ability of antiviral drugs to inhibit HCV replication can be tested *in
vitro* with the HCV replicon system. The replicon system consists of the Huh7 human
hepatoma cell line that has been transfected with subgenomic RNA replicons that direct
constitutive replication of HCV genomic RNAs (Blight, K.J. et al. Science 290:1972-
1974, 2000). Treatment of replicon clones with IFNα at 10 IU/ml reduces the amount
of HCV RNA by 85% compared to untreated control cell lines. The ability of IL-28A
and IL-29 to reduce the amount of HCV RNA produced by the replicon clones in 72
hours indicates the antiviral state conferred upon Huh7 cells by IL-28A/IL-29 treatment
is effective in inhibiting HCV replicon replication, and thereby, very likely effective in
inhibiting HCV replication.

The ability of IL-28A and IL-29 to inhibit HCV replication as
determined by Bayer Branched chain DNA kit, is be done under the following
conditions:

1. IL28 alone at increasing concentrations (6)* up to 1.0 μg/ml
2. IL29 alone at increasing concentrations (6)* up to 1.0 μg/ml
3. PEGIL29 alone at increasing concentrations (6)* up to 1.0 μg/ml
4. IFNα2A alone at 0.3, 1.0, and 3.0 IU/ml
5. Ribavirin alone.

The positive control is IFNα and the negative control is ribavirin.

The cells are stained after 72 hours with Alomar Blue to assess
viablility.

*The concentrations for conditions 1-3 are:

1.0 μg/ml, 0.32 μg/ml, 0.10 μg/ml, 0.032 μg/ml, 0.010 μg/ml, 0.0032
μg/ml.

The replicon clone (BB7) is treated 1X per day for 3 consecutive days with the doses listed above. Total HCV RNA is measured after 72 hours.

Example 15

5   IL-28 and IL-29 have antiviral activity against pathogenic viruses

Two methods are used to assay *in vitro* antiviral activity of IL-28 and IL-29 against a panel of pathogenic viruses including, among others, adenovirus, parainfluenza virus. respiratory syncytial virus, rhino virus, coxsackie virus, influenza virus, vaccinia virus, west nile virus, dengue virus, venezuelan equine encephalitis

10   virus, pichinde virus and polio virus. These two methods are inhibition of virus-induced cytopathic effect (CPE) determined by visual (microscopic) examination of the cells and increase in neutral red (NR) dye uptake into cells. In the CPE inhibition method, seven concentrations of test drug (log10 dilutions, such as 1000, 100, 10, 1, 0.1, 0.01, 0.001 ng/ml) are evaluated against each virus in 96-well flat-bottomed

15   microplates containing host cells. The compounds are added 24 hours prior to virus, which is used at a concentration of approximately 5 to 100 cell culture infectious doses per well, depending upon the virus, which equates to a multiplicity of infection (MOI) of 0.01 to 0.0001 infectious particles per cell. The tests are read after incubation at 37°C for a specified time sufficient to allow adequate viral cytopathic effect to develop. In

20   the NR uptake assay, dye (0.34% concentration in medium) is added to the same set of plates used to obtain the visual scores. After 2 h, the color intensity of the dye absorbed by and subsequently eluted from the cells is determined using a microplate autoreader. Antiviral activity is expressed as the 50% effective (virus-inhibitory) concentration (EC50) determined by plotting compound concentration versus percent inhibition on

25   semilogarithmic graph paper. The EC50/IC50 data in some cases may be determined by appropriate regression analysis software. In general, the EC50s determined by NR assay are two-to fourfold higher than those obtained by the CPE method.

Table 18: Visual Assay

Virus	Cell line	Drug	EC50 Visual	IC50 Visual	SI Visual (IC50/ EC50)
Adenovirus	A549	IL-28A	>10 μg/ml	>10 μg/ml	0
Adenovirus	A549	IL-29	>10 μg/ml	>10 μg/ml	0
Adenovirus	A549	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Parainfluenz a virus	MA-104	IL-28A	>10 μg/ml	>10 μg/ml	0
Parainfluenz a virus	MA-104	IL-29	>10 μg/ml	>10 μg/ml	0
Parainfluenz a virus	MA-104	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Respiratory syncytial virus	MA-104	IL-28A	>10 μg/ml	>10 μg/ml	0
Respiratory syncytial virus	MA-104	IL-29	>10 μg/ml	>10 μg/ml	0
Respiratory syncytial virus	MA-104	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Rhino 2	KB	IL-28A	>10 μg/ml	>10 μg/ml	0
Rhino 2	KB	IL-29	>10 μg/ml	>10 μg/ml	0
Rhino 2	KB	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Rhino 9	HeLa	IL-28A	>10 μg/ml	>10 μg/ml	0
Rhino 9	HeLa	IL-29	>10 μg/ml	>10 μg/ml	0
Rhino 9	HeLa	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Coxsackie B4 virus	KB	IL-28A	>10 μg/ml	>10 μg/ml	0
Coxsackie B4 virus	KB	IL-29	>10 μg/ml	>10 μg/ml	0
Coxsackie B4 virus	KB	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0

Influenza (type A [H3N2])	Maden-Darby Canine Kidney	IL-28A	>10 µg/ml	>10 µg/ml	0
Influenza (type A [H3N2])	Maden-Darby Canine Kidney	IL-29	>10 µg/ml	>10 µg/ml	0
Influenza (type A [H3N2])	Maden-Darby Canine Kidney	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0
Influenza (type A [H3N2])	Vero	IL-28A	0.1 µg/ml	>10 µg/ml	>100
Influenza (type A [H3N2])	Vero	IL-29	>10 µg/ml	>10 µg/ml	0
Influenza (type A [H3N2])	Vero	MetIL-29 C172S-PEG	0.045 µg/ml	>10 µg/ml	>222
Vaccinia virus	Vero	IL-28A	>10 µg/ml	>10 µg/ml	0
Vaccinia virus	Vero	IL-29	>10 µg/ml	>10 µg/ml	0
Vaccinia virus	Vero	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0
West Nile virus	Vero	IL-28A	0.00001 µg/ml	>10 µg/ml	>1,000,000
West Nile virus	Vero	IL-29	0.000032 µg/ml	>10 µg/ml	>300,000
West Nile virus	Vero	MetIL-29 C172S-PEG	0.001 µg/ml	>10 µg/ml	>10,000
Dengue virus	Vero	IL-28A	0.01 µg/ml	>10 µg/ml	>1000
Dengue virus	Vero	IL-29	0.032 µg/ml	>10 µg/ml	>312
Dengue virus	Vero	MetIL-29 C172S-PEG	0.0075 µg/ml	>10 µg/ml	>1330

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Venezuelan equine encephalitis virus	Vero	IL-28A	0.01 µg/ml	>10 µg/ml	>1000
Venezuelan equine encephalitis virus	Vero	IL-29	0.012 µg/ml	>10 µg/ml	>833
Venezuelan equine encephalitis virus	Vero	MetIL-29 C172S-PEG	0.0065 µg/ml	>10 µg/ml	>1538
Pichinde virus	BSC-1	IL-28A	>10 µg/ml	>10 µg/ml	0
Pichinde virus	BSC-1	IL-29	>10 µg/ml	>10 µg/ml	0
Pichinde virus	BSC-1	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0
Polio virus	Vero	IL-28A	>10 µg/ml	>10 µg/ml	0
Polio virus	Vero	IL-29	>10 µg/ml	>10 µg/ml	0
Polio virus	Vero	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0

Table 19: Neutral Red Assay

Virus	Cell line	Drug	EC50 NR	IC50 NR	SI NR (IC50/ EC50)
Adenovirus	A549	IL-28A	>10 µg/ml	>10 µg/ml	0
Adenovirus	A549	IL-29	>10 µg/ml	>10 µg/ml	0
Adenovirus	A549	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0
Parainfluenza virus	MA-104	IL-28A	>10 µg/ml	>10 µg/ml	0
Parainfluenza virus	MA-104	IL-29	>10 µg/ml	>10 µg/ml	0
Parainfluenza virus	MA-104	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0

5

Respiratory syncytial virus	MA-104	IL-28A	>10 μg/ml	>10 μg/ml	0
Respiratory syncytial virus	MA-104	IL-29	>10 μg/ml	>10 μg/ml	0
Respiratory syncytial virus	MA-104	MetIL-29 C172S-PEG	5.47 μg/ml	>10 μg/ml	>2
Rhino 2	KB	IL-28A	>10 μg/ml	>10 μg/ml	0
Rhino 2	KB	IL-29	>10 μg/ml	>10 μg/ml	0
Rhino 2	KB	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Rhino 9	HeLa	IL-28A	1.726 μg/ml	>10 μg/ml	>6
Rhino 9	HeLa	IL-29	0.982 μg/ml	>10 μg/ml	>10
Rhino 9	HeLa	MetIL-29 C172S-PEG	2.051 μg/ml	>10 μg/ml	>5
Coxsackie B4 virus	KB	IL-28A	>10 μg/ml	>10 μg/ml	0
Coxsackie B4 virus	KB	IL-29	>10 μg/ml	>10 μg/ml	0
Coxsackie B4 virus	KB	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Influenza (type A [H3N2])	Maden-Darby Canine Kidney	IL-28A	>10 μg/ml	>10 μg/ml	0
Influenza (type A [H3N2])	Maden-Darby Canine Kidney	IL-29	>10 μg/ml	>10 μg/ml	0
Influenza (type A [H3N2])	Maden-Darby Canine Kidney	MetIL-29 C172S-PEG	>10 μg/ml	>10 μg/ml	0
Influenza (type A [H3N2])	Vero	IL-28A	0.25 μg/ml	>10 μg/ml	>40
Influenza (type A [H3N2])	Vero	IL-29	2 μg/ml	>10 μg/ml	>5
Influenza (type A [H3N2])	Vero	MetIL-29 C172S-PEG	1.4 μg/ml	>10 μg/ml	>7

Vaccinia virus	Vero	IL-28A	>10 µg/ml	>10 µg/ml	0
Vaccinia virus	Vero	IL-29	>10 µg/ml	>10 µg/ml	0
Vaccinia virus	Vero	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0
West Nile virus	Vero	IL-28A	0.0001 µg/ml	>10 µg/ml	>100,000
West Nile virus	Vero	IL-29	0.00025 µg/ml	>10 µg/ml	>40,000
West Nile virus	Vero	MetIL-29 C172S-PEG	0.00037 µg/ml	>10 µg/ml	>27,000
Dengue virus	Vero	IL-28A	0.1 µg/ml	>10 µg/ml	>100
Dengue virus	Vero	IL-29	0.05 µg/ml	>10 µg/ml	>200
Dengue virus	Vero	MetIL-29 C172S-PEG	0.06 µg/ml	>10 µg/ml	>166
Venezuelan equine encephalitis virus	Vero	IL-28A	0.035 µg/ml	>10 µg/ml	>286
Venezuelan equine encephalitis virus	Vero	IL-29	0.05 µg/ml	>10 µg/ml	>200
Venezuelan equine encephalitis virus	Vero	MetIL-29 C172S-PEG	0.02 µg/ml	>10 µg/ml	>500
Pichinde virus	BSC-1	IL-28A	>10 µg/ml	>10 µg/ml	0
Pichinde virus	BSC-1	IL-29	>10 µg/ml	>10 µg/ml	0
Pichinde virus	BSC-1	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0
Polio virus	Vero	IL-28A	>1.672 µg/ml	>10 µg/ml	>6
Polio virus	Vero	IL-29	>10 µg/ml	>10 µg/ml	0
Polio virus	Vero	MetIL-29 C172S-PEG	>10 µg/ml	>10 µg/ml	0

Example 16

IL-28, IL-29, metIL-29-PEG and metIL-29C172S-PEG Stimulate ISG induction in the
Mouse Liver Cell line AML-12

Interferon stimulated genes (ISGs) are genes that are induced by type I
5   interferons (IFNs) and also by the IL-28 and IL-29 family molecules, suggesting that
IFN and IL-28 and IL-29 induce similar pathways leading to antiviral activity. Human
type I IFNs (IFNα1-4 and IFNβ) have little or no activity on mouse cells, which is
thought to be caused by lack of species cross-reactivity. To test if human IL-28 and IL-
29 have effects on mouse cells, ISG induction by human IL-28 and IL-29 was evaluated
10 by real-time PCR on the mouse liver derived cell line AML-12.

AML-12 cells were plated in 6-well plates in complete DMEM media at
a concentration of 2×10^6 cells/well. Twenty-four hours after plating cells, human IL-
28 and IL-29 were added to the culture at a concentration of 20 ng/ml. As a control,
cells were either stimulated with mouse IFNα (positive control) or unstimulated
15 (negative). Cells were harvested at 8, 24, 48 and 72 hours after addition of CHO-
derived human IL-28A (SEQ ID NO:18) or IL-29 (SEQ ID NO:20). RNA was isolated
from cell pellets using RNAEasy-kit® (Qiagen, Valencia, CA). RNA was treated with
DNase (Millipore, Billerica, MA) to clean RNA of any contaminating DNA. cDNA was
generated using Perkin-Elmer RT mix. ISG gene induction was evaluated by real-time
20 PCR using primers and probes specific for mouse OAS, Pkr and Mx1. To obtain
quantitative data, HPRT real-time PCR was duplexed with ISG PCR. A standard curve
was obtained using known amounts of RNA from IFN-stimulated mouse PBLs. All data
are shown as expression relative to internal HPRT expression.

Human IL-28A and IL-29 stimulated ISG induction in the mouse
25 hepatocyte cell line AML-12 and demonstrated that unlike type I IFNs, the IL-28/29
family proteins showed cross-species reactivity.

Table 20

Stimulation	OAS	PkR	Mx1
None	0.001	0.001	0.001
Human IL-28	0.04	0.02	0.06
Human IL-29	0.04	0.02	0.07
Mouse IL-28	0.04	0.02	0.08
Mouse IFNα	0.02	0.02	0.01

All data shown were expressed as fold relative to HPRT gene expression

$$\frac{\text{ng of OAS mRNA}}{\text{ng of HPRT mRNA}} = \text{normalized value of OAS mRNA amount relative to internal housekeeping gene, HPRT}$$

As an example, the data for the 48 hour time point is shown.

Table 21

AML12's

	Mx1 Fold Induction	OAS Fold Induction	Pkr Fold Induction
MetIL-29-PEG	728	614	8
MetIL-29C172S-PEG	761	657	8

Cells were stimulated with 20 ng/ml metIL-29-PEG or metIL-29C172S-PEG for 24 hours.

Data shown is normalized to HPRT and shown as fold induction over unstimulated cells.

Example 17

ISGs are Efficiently Induced in Spleens of Transgenic Mice Expressing Human IL-29

Transgenic (Tg) mice were generated expressing human IL-29 under the control of the Eu-lck promoter. To study if human IL-29 has biological activity *in vivo* in mice, expression of ISGs was analyzed by real-time PCR in the spleens of Eu-lck IL-29 transgenic mice.

Transgenic mice (C3H/C57BL/6) were generated using a construct that expressed the human IL-29 gene under the control of the Eu-lck promoter. This promoter is active in T cells and B cells. Transgenic mice and their non-transgenic littermates (n=2/gp) were sacrificed at about 10 weeks of age. Spleens of mice were isolated. RNA was isolated from cell pellets using RNAEasy-kit® (Qiagen). RNA was treated with DNase to clean RNA of any contaminating DNA. cDNA was generated using Perkin-Elmer RT® mix. ISG gene induction was evaluated by real-time PCR using primers and probes (5' FAM, 3' NFQ) specific for mouse OAS, Pkr and Mx1. To obtain quantitative data, HPRT real-time PCR was duplexed with ISG PCR. Furthermore, a standard curve was obtained using known amounts of IFN stimulated mouse PBLs. All data are shown as expression relative to internal HPRT expression.

Spleens isolated from IL-29 Tg mice showed high induction of ISGs OAS, Pkr and Mx1 compared to their non-Tg littermate controls suggesting that human IL-29 is biologically active in vivo in mice.

Table 22

Mice	OAS	PkR	Mx1
Non-Tg	4.5	4.5	3.5
IL-29 Tg	12	8	21

All data shown are fold expresssion relative to HPRT gene expresssion. The average expression in two mice is shown

5   Example 18

Human IL-28 and IL-29 Protein Induce ISG Gene Expression In Liver, Spleen and Blood of Mice

To determine whether human IL-28 and IL-29 induce interferon stimulated genes *in vivo*, CHO-derived human IL-28A and IL-29 protein were injected 10   into mice. In addition, *E. coli* derived IL-29 was also tested in *in vivo* assays as described above using MetIL-29C172S-PEG and MetIL-29-PEG. At various time points and at different doses, ISG gene induction was measured in the blood, spleen and livers of the mice.

C57BL/6 mice were injected i.p or i.v with a range of doses (10 µg – 250 15   µg) of CHO-derived human IL-28A and IL-29 or MetIL-29C172S-PEG and MetIL-29C16-C113-PEG. Mice were sacrificed at various time points (1hr – 48hr). Spleens and livers were isolated from mice, and RNA was isolated. RNA was also isolated from the blood cells. The cells were pelleted and RNA isolated from pellets using RNAEasy®-kit (Qiagen). RNA was treated with DNase (Amicon) to rid RNA of any 20   contaminating DNA. cDNA was generated using Perkin-Elmer RT mix (Perkin-Elmer). ISG gene induction was measured by real-time PCR using primers and probes specific for mouse OAS, Pkr and Mx1. To obtain quantitative data, HPRT real-time PCR was duplexed with ISG PCR. A standard curve was calculated using known amounts of IFN-stimulated mouse PBLs. All data are shown as expression relative to internal 25   HPRT expression.

Human IL-29 induced ISG gene expression (OAS, Pkr, Mx1) in the livers, spleen and blood of mice in a dose dependent manner. Expression of ISGs peaked between 1-6 hours after injection and showed sustained expression above control mice upto 48 hours. In this experiment, human IL-28A did not induce ISG gene 30   expression.

Table 23

Injection	OAS- 1hr	OAS-6hr	OAS-24hr	OAS-48hr
None - liver	1.6	1.6	1.6	1.6
IL-29 liver	2.5	4	2.5	2.8
None - spleen	1.8	1.8	1.8	1.8
IL-29 - spleen	4	6	3.2	3.2
None - blood	5	5	5	5
IL-29 blood	12	18	11	10

Results shown are fold expression relative to HPRT gene expression. A sample data set for IL-29 induced OAS in liver at a single injection of 250 µg i.v. is shown. The data shown is the average expression from 5 different animals/group.

Table 24

Injection	OAS (24hr)
None	1.8
IL-29 10 µg	3.7
IL-29 50 µg	4.2
IL-29 250 µg	6

Table 25

	MetIL-29-PEG				MetIL-29C172S-PEG				Naive
	3hr	6hr	12hr	24hr	3hr	6hr	12hr	24hr	24hr
PKR	18.24	13.93	4.99	3.77	5.29	5.65	3.79	3.55	3.70
OAS	91.29	65.93	54.04	20.81	13.42	13.02	10.54	8.72	6.60
Mx1	537.51	124.99	33.58	35.82	27.89	29.34	16.61	0.00	10.98

Mice were injected with 100 µg of proteins i.v. Data shown is fold expression over HPRT expression from livers of mice. Similar data was obtained from blood and spleens of mice.

Example 19

IL-28 and IL-29 Induce ISG Protein In Mice

To analyze of the effect of human IL-28 and IL-29 on induction of ISG protein (OAS), serum and plasma from IL-28 and IL-29 treated mice were tested for OAS activity.

C57BL/6 mice were injected i.v with PBS or a range of concentrations (10 µg-250 µg) of human IL-28 or IL-29. Serum and plasma were isolated from mice at varying time points, and OAS activity was measured using the OAS radioimmunoassay (RIA) kit from Eiken Chemicals (Tokyo, Japan).

IL-28 and IL-29 induced OAS activity in the serum and plasma of mice showing that these proteins are biologically active *in vivo*.

Table 26

Injection	OAS-1hr	OAS-6hr	OAS-24hr	OAS-48hr
None	80	80	80	80
IL-29	80	80	180	200

OAS activity is shown at pmol/dL of plasma for a single concentration
5   (250 μg) of human IL-29.

Example 20
IL-28 and IL-29 inhibit Adenoviral pathology in mice

To test the antiviral activities of IL-28 and IL-29 against viruses that
10   infect the liver, the test samples were tested in mice against infectious adenoviral vectors expressing an internal green fluorescent protein (GFP) gene. When injected intravenously, these viruses primarily target the liver for gene expression. The adenoviruses are replication deficient, but cause liver damage due to inflammatory cell infiltrate that can be monitored by measurement of serum levels of liver enzymes like
15   AST and ALT, or by direct examination of liver pathology.

C57Bl/6 mice were given once daily intraperitoneal injections of 50 μg mouse IL-28 (zcyto24 as shown in SEQ ID NO:9) or metIL-29C172S- PEG for 3 days. Control animals were injected with PBS. One hour following the 3rd dose, mice were given a single bolus intravenous tail vein injection of the adenoviral vector, AdGFP (1
20   X 10^9 plaque-forming units (pfu)). Following this, every other day mice were given an additional dose of PBS, mouse IL-28 or metIL-29C172S- PEG for 4 more doses (total of 7 doses). One hour following the final dose of PBS, mouse IL-28 or metIL-29C172S- PEG mice were terminally bleed and sacrificed. The serum and liver tissue were analyzed. Serum was analyzed for AST and ALT liver enzymes. Liver was
25   isolated and analyzed for GFP expression and histology. For histology, liver specimens were fixed in formalin and then embedded in paraffin followed by H&E staining. Sections of liver that had been blinded to treat were examined with a light microscope. Changes were noted and scored on a scale designed to measure liver pathology and inflammation.
30   Mouse IL-28 and IL-29 inhibited adenoviral infection and gene expression as measured by liver fluorescence. PBS-treated mice (n=8) had an average relative liver fluorescence of 52.4 (arbitrary units). In contrast, IL-28-treated mice

(n=8) had a relative liver fluorescence of 34.5, and IL-29-treated mice (n=8) had a relative liver fluorescence of 38.9. A reduction in adenoviral infection and gene expression led to a reduced liver pathology as measured by serum ALT and AST levels and histology. PBS-treated mice (n=8) had an average serum AST of 234 U/L

5   (units/liter) and serum ALT of 250 U/L. In contrast, IL-28-treated mice (n=8) had an average serum AST of 193 U/L and serum ALT of 216 U/L, and IL-29-treated mice (n=8) had an average serum AST of 162 U/L and serum ALT of 184 U/L. In addition, the liver histology indicated that mice given either mouse IL-28 or IL-29 had lower liver and inflammation scores than the PBS-treated group. The livers from the IL-29

10 group also had less proliferation of sinusoidal cells, fewer mitotic figures and fewer changes in the hepatocytes (e.g. vacuolation, presence of multiple nuclei, hepatocyte enlargement) than in the PBS treatment group. These data demonstrate that mouse IL-28 and IL-29 have antiviral properties against a liver-trophic virus.

15 Example 21
    LCMV Models
              Lymphocytic choriomeningitis virus (LCMV) infections in mice mice are an excellent model of acture and chronic infection. These models are used to evaluate the effect of cytokines on the antiviral immune response and the effects IL-28

20 and IL-29 have viral load and the antiviral immune response. The two models used are: LCMV Armstrong (acute) infection and LCMV Clone 13 (chronic) infection. (See, e.g., Wherry et al., J. Virol. 77:4911-4927, 2003; Blattman et al., Nature Med. 9(5):540-547, 2003; Hoffman et al., J. Immunol. 170:1339-1353, 2003.) There are three stages of CD8 T cell development in response to virus: 1) expansion, 2) contraction, and 3)

25 memory (acute model). IL-28 or IL-29 is injected during each stage for both acute and chronic models. In the chronic model, IL-28 or IL-29 is injected 60 days after infection to assess the effect of IL-28 or IL-29 on persistent viral load. For both acute and chronic models, IL-28 or IL-29 is injected, and the viral load in blood, spleen and liver is examined. Other paramenter that can be examined include: tetramer staining by flow

30 to count the number of LCMV-specific CD8+ T cells; the ability of tetramer+ cells to produce cytokines when stimulated with their cognate LCMV antigen; and the ability of LCMV-specific CD8+ T cells to proliferate in response to their cognate LCMV antigen. LCMV-specific T cells are phenotyped by flow cytometry to assess the cells activation and differentiation state. Also, the ability of LCMV-specific CTL to lyse

35 target cells bearing their cognate LCMV antigen is examined. The number and function of LCMV-specific CD4+ T cells is also assessed.

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A reduction in viral load after treatment with IL-28 or IL-29 is determined. A 50% reduction in viral load in any organ, especially liver, would be significant. For IL-28 or IL-29 treated mice, a 20% increase in the percentage of tetramer positive T cells that proliferate, make cytokine, or display a mature phenotype relative to untreated mice would also be considered significant.

IL-28 or IL-29 injection leading to a reduction in viral load is due to more effective control of viral infection especially in the chronic model where untreated the viral titers remain elevated for an extended period of time. A two fold reduction in viral titer relative to untreated mice is considered significant.

Example 22
Influenza Model of Acute Viral Infection
A.   Preliminary Experiment to test antiviral activity.

To determine the antiviral activity of IL-28 or IL-29 on acute infection by *Influenza* virus, an *in vivo* study using influenza infected c57B1/6 mice is performed using the following protocol:

Animals: 6 weeks-old female BALB/c mice (Charles River) with 148 mice, 30 per group.

Groups:

(1) Absolute control (not infected) to run in parallel for antibody titre and histopathology (2 animals per group).

(2) Vehicle (i.p.) saline

(3) Amantadine (positive control) 10 mg/day during 5 days (per os) starting 2 hours before infection

(4) IL-28 or IL-29 treated (5 µg, i.p. starting 2 hours after infection)

(5) IL-28 or IL-29 (25 µg, i.p. starting 2 hours after infection)

(6) IL-28 or IL-29 (125 µg, i.p. starting 2 hours after infection)

Day 0 – Except for the absolute controls, all animals infected with Influenza virus

For viral load (10 at LD50)

For immunology workout (LD30)

Day 0 – 9 – daily injections of IL-28 or IL-29 (i.p.)

Body weight and general appearance recorded (3 times/week)

Day 3 – sacrifice of 8 animals per group

Viral load in right lung (TCID50)

Histopathology in left lung

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Blood sample for antibody titration

Day 10 – sacrifice of all surviving animals collecting blood samples for antibody titration, isolating lung lymphocytes (4 pools of 3) for direct CTL assay (in all 5 groups), and quantitative immunophenotyping for the following markers: CD3/CD4, CD3/CD8, CD3/CD8/CD11b, CD8/CD44/CD62L, CD3/DX5, GR-1/F480, and CD19.

Study No.2

Efficacy study of IL-28 or IL-29 in C57Bl/6 mice infected with mouse-adapted virus is done using 8 weeks-old female C57Bl/6 mice (Charles River).

Group 1: Vehicle (i.p.)

Group 2: Positive control: Anti-influenza neutralizing antibody (goat anti-influenza A/USSR (H1N1) (Chemicon International, Temecula, CA); 40 µg/mouse at 2 h and 4 h post infection (10 µl intranasal)

Group 3: IL-28 or IL-29 (5 µg, i.p.)

Group 4: IL-28 or IL-29 (25 µg, i.p.)

Group 5: IL-28 or IL-29 (125 µg, i.p.)

Following-life observations and immunological workouts are prepared:

Day 0 – all animals infected with Influenza virus (dose determined in experiment 2)

Day 0 – 9 – daily injections of IL-28 or IL-29 (i.p.)

Body weight and general appearance recorded every other day

Day 10 – sacrifice of surviving animals and perform viral assay to determine viral load in lung.

Isolation of lung lymphocytes (for direct CTL assay in the lungs using EL-4 as targets and different E:T ratio (based on best results from experiments 1 and 2).

Tetramer staining: The number of CD8+ T cells binding MHC Class I tetramers containing influenza A nucleoprotein (NP) epitope are assessed using complexes of MHC class I with viral peptides: FLU-NP$_{366-374}$/D^b (ASNENMETM), (LMCV peptide/D^b).

Quantitative immunophenotyping of the following: CD8, tetramer, intracellular IFNγ, NK1.1, CD8, tetramer, CD62L, CD44, CD3(+ or -), NK1.1(+), intracellular IFNγ, CD4, CD8, NK1.1, DX5, CD3 (+ or -), NK1.1, DX5, tetramer, Single colour samples for cytometer adjustment.

55

Survival/Re-challenge Study

Day 30: Survival study with mice are treated for 9 days with different doses of IL-28 or IL-29 or with positive anti-influenza antibody control. Body weight and antibody production in individual serum samples (Total, IgG1, IgG2a, IgG2b) are measured.

Re-challenge study:

Day 0: Both groups will be infected with A/PR virus (1LD30).

Group 6 will not be treated.

Group 7 will be treated for 9 days with 125 µg of IL-28 or IL-29.

Day 30: Survival study

Body weight and antibody production in individual serum samples (Total, IgG1, IgG2a, IgG2b) are measured.

Day 60: Re-challenge study

Survivors in each group will be divided into 2 subgroups

Group 6A and 7A will be re-challenge with A/PR virus (1 LD30)

Group 6B and 7B will be re-challenge with A/PR virus (1 LD30).

Both groups will be followed up and day of sacrifice will be determined. Body weight and antibody production in individual serum samples (Total, IgG1, IgG2a, IgG2b) are measured.

Example 21
IL-28 and IL-29 have Antiviral Activity Against Hepatitis B virus (HBV) in vivo.

A transgenic mouse model (Guidotti et al., J. Virology 69:6158-6169, 1995) supports the replication of high levels of infectious HBV and has been used as a chemotherapeutic model for HBV infection. Transgenic mice are treated with antiviral drugs and the levels of HBV DNA and RNA are measured in the transgenic mouse liver and serum following treatment. HBV protein levels can also be measured in the transgenic mouse serum following treatment. This model has been used to evaluate the effectiveness of lamivudine and IFN-α in reducing HBV viral titers..

HBV TG mice (male) are given intraperitoneal injections of 2.5, 25 or 250 micrograms IL-28 or IL-29 every other day for 14 days (total of 8 doses). Mice are bled for serum collection on day of treatment (day 0) and day 7. One hour following the final dose of IL-29 mice undergo a terminal bleed and are sacrificed. Serum and liver are analyzed for liver HBV DNA, liver HBV RNA, serum HBV DNA, liver HBc, serum Hbe and serum HBs.

Reduction in liver HBV DNA, liver HBV RNA, serum HBV DNA, liver HBc, serum Hbe or serum HBs in response to IL-28 or IL-29 reflects antiviral activity of these compounds against HBV.

Example 22
IL-28 and IL-29 inhibit human herpesvirus-8 (HHV-8) replication in BCBL-1 cells

The antiviral activities of IL-28 and IL-29 were tested against HHV-8 in an *in vitro* infection system using a B-lymphoid cell line, BCBL-1.

In the HHV-8 assay the test compound and a ganciclovir control were assayed at five concentrations each, diluted in a half-log series. The endpoints were TaqMan PCR for extracellular HHV-8 DNA (IC50) and cell numbers using CellTiter96® reagent (TC50; Promega, Madison, WI). Briefly, BCBL-1 cells were plated in 96-well microtiter plates. After 16-24 hours the cells were washed and the medium was replaced with complete medium containing various concentrations of the test compound in triplicate. Ganciclovir was the positive control, while media alone was a negative control (virus control, VC). Three days later the culture medium was replaced with fresh medium containing the appropriately diluted test compound. Six days following the initial administration of the test compound, the cell culture supernatant was collected, treated with pronase and DNAse and then used in a real-time quantitative TaqMan PCR assay. The PCR-amplified HHV-8 DNA was detected in real-time by monitoring increases in fluorescence signals that result from the exonucleolytic degradation of a quenched fluorescent probe molecule that hybridizes to the amplified HHV-8 DNA. For each PCR amplification, a standard curve was simultaneously generated using dilutions of purified HHV-8 DNA. Antiviral activity was calculated from the reduction in HHV-8 DNA levels (IC_{50}). A novel dye uptake assay was then employed to measure cell viability which was used to calculate toxicity (TC_{50}). The therapeutic index (TI) is calculated as TC_{50}/IC_{50}.

IL-28 and IL-29 inhibit HHV-8 viral replication in BCBL-1 cells. IL-28A had an IC_{50} of 1 μg/ml and a TC_{50} of >10 μg/ml (TI >10). IL-29 had an IC_{50} of 6.5 μg/ml and a TC_{50} of >10 μg/ml (TI >1.85). MetIL-29C172S-PEG had an IC_{50} of 0.14 μg/ml and a TC_{50} of >10 μg/ml (TI >100).

Example 23

IL-28 and IL-29 antiviral activity against Epstein Barr Virus (EBV)

The antiviral activities of IL-28 and IL-29 are tested against EBV in an *in vitro* infection system in a B-lymphoid cell line, P3HR-1. In the EBV assay the test

compound and a control are assayed at five concentrations each, diluted in a half-log series. The endpoints are TaqMan PCR for extracellular EBV DNA (IC50) and cell numbers using CellTiter96® reagent (TC50; Promega). Briefly, P3HR-1 cells are plated in 96-well microtiter plates. After 16-24 hours the cells are washed and the

5   medium is replaced with complete medium containing various concentrations of the test compound in triplicate. In addition to a positive control, media alone is added to cells as a negative control (virus control, VC). Three days later the culture medium is replaced with fresh medium containing the appropriately diluted test compound. Six days following the initial administration of the test compound, the cell culture supernatant is

10 collected, treated with pronase and DNAse and then used in a real-time quantitative TaqMan PCR assay. The PCR-amplified EBV DNA is detected in real-time by monitoring increases in fluorescence signals that result from the exonucleolytic degradation of a quenched fluorescent probe molecule that hybridizes to the amplified EBV DNA. For each PCR amplification, a standard curve was simultaneously

15 generated using dilutions of purified EBV DNA. Antiviral activity is calculated from the reduction in EBV DNA levels (IC_{50}). A novel dye uptake assay was then employed to measure cell viability which was used to calculate toxicity (TC_{50}). The therapeutic index (TI) is calculated as TC_{50}/IC_{50}.

20 Example 24

IL-28 and IL-29 antiviral activity against Herpes Simplex Virus-2 (HSV-2)

The antiviral activities of IL-28 and IL-29 were tested against HSV-2 in an *in vitro* infection system in Vero cells. The antiviral effects of IL-28 and IL-29 were assessed in inhibition of cytopathic effect assays (CPE). The assay involves the killing

25 of Vero cells by the cytopathic HSV-2 virus and the inhibition of cell killing by IL-28 and IL-29. The Vero cells are propagated in Dulbecco's modified essential medium (DMEM) containing phenol red with 10% horse serum, 1% glutamine and 1% penicillin-streptomycin, while the CPE inhibition assays are performed in DMEM without phenol red with 2% FBS, 1% glutamine and 1% Pen-Strep. On the day

30 preceding the assays, cells were trypsinized (1% trypsin-EDTA), washed, counted and plated out at 10^4 cells/well in a 96-well flat-bottom BioCoat® plates (Fisher Scientific, Pittsburgh, PA) in a volume of 100 μl/well. The next morning, the medium was removed and a pre-titered aliquot of virus was added to the cells. The amount of virus used is the maximum dilution that would yield complete cell killing (>80%) at the time

35 of maximal CPE development. Cell viability is determined using a CellTiter 96® reagent (Promega) according to the manufacturer's protocol, using a Vmax plate reader

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(Molecular Devices, Sunnyvale, CA). Compounds are tested at six concentrations each, diluted in assay medium in a half-log series. Acyclovir was used as a positive control. Compounds are added at the time of viral infection. The average background and drug color-corrected data for percent CPE reduction and percent cell viability at each

5   concentration are determined relative to controls and the IC_{50} calculated relative to the TC_{50}.

IL-28A, IL-29 and MetIL-29C172S-PEG did not inhibit cell death (IC_{50} of >10ug/ml) in this assay. There was also no antiviral activity of IFNα in the is assay.

10   From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

1.   A method of treating a viral infection comprising administering to a mammal with a viral infection causing liver inflammation a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue 22 to residue 205, wherein after administration of the polypeptide the viral infection level or the liver inflammation is reduced.

2.   The method of claim 1, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:18 from residue 1 to residue 175.

3.   The method of claim 1, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO: 24 or SEQ ID NO:26.

4.   The method of claim 1, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:28 or SEQ ID NO:30.

5.   The method of claim 1, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:36.

6.   The method of claim 1, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

7.   The method of claim 1, wherein reduction in the viral infection level is measured as a decrease in viral load, an increase in antiviral antibodies, a decrease in serological levels of alanine aminotransferase or histological improvement.

8.   The method of claim 1, wherein the mammal is a human.

9.   The method of claim 1, wherein the viral infection is a hepatitis B virus or hepatitis C virus infection or a hepatitis B virus infection.

10.   A method of treating a viral infection comprising administering to a mammal with a viral infection causing liver inflammation a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID

NO:4 from amino residue 20 to residue 200, wherein after administration of the polypeptide the viral infection level or the liver inflammation is reduced.

11.   The method of claim 10, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:20 from residue 1 to residue 181.

12.   The method of claim 10, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO: 32 or SEQ ID NO:34.

13.   The method of claim 10, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:38.

14.   The method of claim 10, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

15.   The method of claim 10, wherein reduction in the viral infection level is measured as a decrease in viral load, an increase in antiviral antibodies, a decrease in serological levels of alanine aminotransferase or histological improvement.

16.   The method of claim 10, wherein the mammal is a human.

17.   The method of claim 10, wherein the viral infection is a hepatitis B virus infection or hepatitis C virus infection.

18.   A method of treating liver inflammation comprising administering to a mammal in need thereof a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue 22 to residue 205, wherein after administration of the polypeptide the liver inflammation is reduced.

19.   The method of claim 18, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:18 from residue 1 to residue 175.

20.   The method of claim 18, wherein the polypeptide comprises an amino acid as shown in SEQ ID NO:24 or SEQ ID NO:26.

21.   The method of claim 18, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:28 or SEQ ID NO:30.

22.   The method of claim 18, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:36.

23.   The method of claim 18, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

24.   The method of claim 18, wherein the mammal is human.

25.   The method of claim 18, wherein the liver inflammation is associated with a hepatitis B virus infection or a hepatitis C virus infection.

26.   A method of treating liver inflammation comprising administering to a mammal in need thereof a therapeutically effective amount of a polypeptide comprising an amino acide sequence that has at least 95% identity to SEQ ID NO:4 from amino acid residue 22 to residue 205, wherein after administration of the polypeptide the liver inflammation is reduced.

27.   The method of claim 26, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:20 from residue 1 to residue 181.

28.   The method of claim 26, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:32 or SEQ ID NO:34.

29.   The method of claim 26, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:38.

30.   The method of claim 26, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

31.   The method of claim 26, wherein the mammal is human.

32.   The method of claim 26, wherein the liver inflammation is associated with a hepatitis B virus infection or a hepatitis C virus infection.

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33.   A method of treating a viral infection comprising administering to an immunocompromised mammal with a viral infection a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue 22 to residue 205, wherein after administration of the polypeptide the viral infection is reduced.

34.   The method of claim 33, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:18 from residue 1 to 175.

35.   The method of claim 33, wherein the polypeptide comprises and amino acid sequence as shown in SEQ ID NO:24 or SEQ ID NO:26.

36.   The method of claim 33, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:28 or SEQ ID NO:30.

37.   The method of claim 33, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:36.

38.   The method of claim 33, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

39.   The method of claim 33, wherein reduction in the viral infection is measured as a decrease in viral load, an increase in antiviral antibodies, a decrease in serological levels of alanine aminotransferase or histological improvement.

40.   A method of treating a viral infection comprising administering to an immunocompromised mammal with a viral infection a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:4 from amino acid residue 20 to residue 200, wherein after administration of the polypeptide the viral infection is reduced.

41.   The method of claim 40, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:20 from residue 1 to 181.

42.   The method of claim 40, wherein the polypeptide comprises and amino acid sequence as shown in SEQ ID NO:32 or SEQ ID NO:34.

43.   The method of claim 40, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:38.

44.   The method of claim 40, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

45.   The method of claim 40, wherein reduction in the viral infection is measured as a decrease in viral load, an increase in antiviral antibodies, a decrease in serological levels of alanine aminotransferase or histological improvement.

46.   The method of claim 40, wherein the mammal is human.

47.   A method of treating liver inflammation comprising administering to an immunocompromised mammal with liver inflammation a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:2 from amino acid residue 22 to residue 205, wherein after administration the liver inflammation is reduced.

48.   The method of claim 47, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:18 from residue 1 to 175.

49.   The method of claim 47, wherein the polypeptide comprises and amino acid sequence as shown in SEQ ID NO:24 or SEQ ID NO:26.

50.   The method of claim 47, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:28 or SEQ ID NO:30.

51.   The method of claim 47, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:36.

52.   The method of claim 47, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

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53.   A method of treating liver inflammation comprising administering to an immunocompromised mammal with liver inflammation a therapeutically effective amount of a polypeptide comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:4 from amino acid residue 20 to residue 200, wherein after administration of the polypeptide the liver inflammation is reduced.

54.   The method of claim 53, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:20 from residue 1 to 181.

55.   The method of claim 53, wherein the polypeptide comprises and amino acid sequence as shown in SEQ ID NO:32 or SEQ ID NO:34.

56.   The method of claim 53, wherein the polypeptide comprises an amino acid sequence as shown in SEQ ID NO:38.

57.   The method of claim 53, wherein the polypeptide is conjugated to a polyalkyl oxide moiety.

58.   The method of claim 47, wherein the mammal has a cytopenia.

59.   The method of claim 53, wherein the mammal has cytopenia.

60.   The method of claim 58, wherein the cytopenia is selected from the group consisting of leukocyte deficiency, neutropenia, thrombocytopenia, and anemia.

61.   The method of claim 59, wherein the cytopenia is selected from the group consisting of leukocyte deficiency, neutropenia, thrombocytopenia and anemia.

SEQUENCE LISTING

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<120> METHODS FOR TREATING VIRAL INFECTION
      USING IL-28 AND IL-29

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            100                 105                 110

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Pro Ala Leu Val Asp Val Leu Asp Gln Pro Leu His Thr Leu His His
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cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag gag tcc cct    528
His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Pro
                165                 170                 175

ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc ctc acg    576
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
            180                 185                 190

cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc tga            618
Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val *
            195                 200                 205


<210> 2
<211> 205
<212> PRT
<213> Homo sapiens

<400> 2
Met Thr Gly Asp Cys Thr Pro Val Leu Val Leu Met Ala Ala Val Leu
1               5                   10                  15
Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu His Gly Ala Leu Pro
            20                  25                  30
Asp Ala Arg Gly Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln
            35                  40                  45
Glu Leu Gln Ala Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu
    50                  55                  60
Leu Leu Lys Asp Cys Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp
65                  70                  75                  80
Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala
                85                  90                  95
Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp
            100                 105                 110
Pro Ala Leu Val Asp Val Leu Asp Gln Pro Leu His Thr Leu His His
            115                 120                 125
Ile Leu Ser Gln Phe Arg Ala Cys Val Ser Arg Gln Gly Leu Gly Thr
            130                 135                 140
Gln Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly Arg Leu
145                 150                 155                 160
His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Pro
                165                 170                 175
```

```
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
            180                     185                 190
Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
        195                 200                 205
```

<210> 3
<211> 603
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(603)

<221> misc_feature
<222> (0)...(0)
<223> IL-29

<400> 3
```
atg gct gca gct tgg acc gtg gtg ctg gtg act ttg gtg cta ggc ttg     48
Met Ala Ala Ala Trp Thr Val Val Leu Val Thr Leu Val Leu Gly Leu
1               5                   10                  15

gcc gtg gca ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag     96
Ala Val Ala Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys
                20                  25                  30

ggc tgc cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg    144
Gly Cys His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala
            35                  40                  45

agc ttc aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa    192
Ser Phe Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys
        50                  55                  60

aac tgg agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg    240
Asn Trp Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg
65                  70                  75                  80

ctt ctc cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc    288
Leu Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala
                85                  90                  95

ctg acg ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac    336
Leu Thr Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp
            100                 105                 110

gtc cta gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc    384
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
            115                 120                 125

cag gcc tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc    432
Gln Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly
        130                 135                 140

cgc ctc cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag    480
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
145                 150                 155                 160
```

```
tcc gct ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc    528
Ser Ala Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
                165             170             175

ctc acg cga gac ctc aaa tat gtg gcc gat ggg gac ctg tgt ctg aga    576
Leu Thr Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg
            180             185             190

acg tca acc cac cct gag tcc acc tga                                603
Thr Ser Thr His Pro Glu Ser Thr  *
        195             200
```

<210> 4
<211> 200
<212> PRT
<213> Homo sapiens

<400> 4

```
Met Ala Ala Ala Trp Thr Val Val Leu Val Thr Leu Val Leu Gly Leu
 1               5                  10                  15
Ala Val Ala Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys
            20                  25                  30
Gly Cys His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala
        35                  40                  45
Ser Phe Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys
    50                  55                  60
Asn Trp Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg
65                  70                  75                  80
Leu Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala
                85                  90                  95
Leu Thr Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp
            100                 105                 110
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
            115                 120                 125
Gln Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly
    130                 135                 140
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
145                 150                 155                 160
Ser Ala Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
                165                 170                 175
Leu Thr Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg
            180                 185                 190
Thr Ser Thr His Pro Glu Ser Thr
            195                 200
```

<210> 5
<211> 615
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(615)

<221> misc_feature
<222> (0)...(0)
<223> IL-28B

<400> 5

```
atg acc ggg gac tgc atg cca gtg ctg gtg ctg atg gcc gca gtg ctg     48
Met Thr Gly Asp Cys Met Pro Val Leu Val Leu Met Ala Ala Val Leu
1               5                   10                  15

acc gtg act gga gca gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg     96
Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro
            20                  25                  30

gat gca agg ggc tgc cac ata gcc cag ttc aag tcc ctg tct cca cag    144
Asp Ala Arg Gly Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln
        35                  40                  45

gag ctg cag gcc ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt    192
Glu Leu Gln Ala Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu
    50                  55                  60

ctg ctg aag gac tgc aag tgc cgc tcc cgc ctc ttc ccc agg acc tgg    240
Leu Leu Lys Asp Cys Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp
65                  70                  75                  80

gac ctg agg cag ctg cag gtg agg gag cgc ccc gtg gct ttg gag gct    288
Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala
                85                  90                  95

gag ctg gcc ctg acg ctg aag gtt ctg gag gcc acc gct gac act gac    336
Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp
            100                 105                 110

cca gcc ctg ggg gat gtc ttg gac cag ccc ctt cac acc ctg cac cat    384
Pro Ala Leu Gly Asp Val Leu Asp Gln Pro Leu His Thr Leu His His
            115                 120                 125

atc ctc tcc cag ctc cgg gcc tgt gtg agt cgt cag ggc ccg ggc acc    432
Ile Leu Ser Gln Leu Arg Ala Cys Val Ser Arg Gln Gly Pro Gly Thr
    130                 135                 140

cag atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc cgc ctc    480
Gln Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly Arg Leu
145                 150                 155                 160

cac cat tgg ctg cac cgg ctc cag gag gcc cca aaa aag gag tcc cct    528
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Pro
                165                 170                 175

ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc ctc acg    576
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
            180                 185                 190

cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc                 615
Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
            195                 200                 205
```

<210> 6
<211> 205
<212> PRT
<213> Homo sapiens

<400> 6

```
Met Thr Gly Asp Cys Met Pro Val Leu Val Leu Met Ala Ala Val Leu
1               5                   10                  15
```

6

```
Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro
            20                  25                  30
Asp Ala Arg Gly Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln
        35                  40                  45
Glu Leu Gln Ala Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu
    50                  55                  60
Leu Leu Lys Asp Cys Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp
65                  70                  75                  80
Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala
                85                  90                  95
Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp
            100                 105                 110
Pro Ala Leu Gly Asp Val Leu Asp Gln Pro Leu His Thr Leu His His
        115                 120                 125
Ile Leu Ser Gln Leu Arg Ala Cys Val Ser Arg Gln Gly Pro Gly Thr
    130                 135                 140
Gln Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly Arg Leu
145                 150                 155                 160
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Pro
                165                 170                 175
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
            180                 185                 190
Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
        195                 200                 205


<210> 7
<211> 633
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (22)...(630)

<400> 7
tcacagaccc cggagagcaa c atg aag cca gaa aca gct ggg ggc cac atg      51
                         Met Lys Pro Glu Thr Ala Gly Gly His Met
                           1               5                  10

ctc ctc ctg ctg ttg cct ctg ctg ctg gcc gca gtg ctg aca aga acc    99
Leu Leu Leu Leu Leu Pro Leu Leu Leu Ala Ala Val Leu Thr Arg Thr
                15                  20                  25

caa gct gac cct gtc ccc agg gcc acc agg ctc cca gtg gaa gca aag   147
Gln Ala Asp Pro Val Pro Arg Ala Thr Arg Leu Pro Val Glu Ala Lys
            30                  35                  40

gat tgc cac att gct cag ttc aag tct ctg tcc cca aaa gag ctg cag   195
Asp Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Lys Glu Leu Gln
        45                  50                  55

gcc ttc aaa aag gcc aag gat gcc atc gag aag agg ctg ctt gag aag   243
Ala Phe Lys Lys Ala Lys Asp Ala Ile Glu Lys Arg Leu Leu Glu Lys
    60                  65                  70

gac ctg agg tgc agt tcc cac ctc ttc ccc agg gcc tgg gac ctg aag   291
Asp Leu Arg Cys Ser Ser His Leu Phe Pro Arg Ala Trp Asp Leu Lys
75                  80                  85                  90
```

```
cag ctg cag gtc caa gag cgc ccc aag gcc ttg cag gct gag gtg gcc   339
Gln Leu Gln Val Gln Glu Arg Pro Lys Ala Leu Gln Ala Glu Val Ala
                95               100              105

ctg acc ctg aag gtc tgg gag aac atg act gac tca gcc ctg gcc acc   387
Leu Thr Leu Lys Val Trp Glu Asn Met Thr Asp Ser Ala Leu Ala Thr
            110              115              120

atc ctg ggc cag cct ctt cat aca ctg agc cac att cac tcc cag ctg   435
Ile Leu Gly Gln Pro Leu His Thr Leu Ser His Ile His Ser Gln Leu
            125              130              135

cag acc tgt aca cag ctt cag gcc aca gca gag ccc agg tcc ccg agc   483
Gln Thr Cys Thr Gln Leu Gln Ala Thr Ala Glu Pro Arg Ser Pro Ser
            140              145              150

cgc cgc ctc tcc cgc tgg ctg cac agg ctc cag gag gcc cag agc aag   531
Arg Arg Leu Ser Arg Trp Leu His Arg Leu Gln Glu Ala Gln Ser Lys
155              160              165              170

gag acc cct ggc tgc ctg gag gcc tct gtc acc tcc aac ctg ttt cgc   579
Glu Thr Pro Gly Cys Leu Glu Ala Ser Val Thr Ser Asn Leu Phe Arg
                175              180              185

ctg ctc acc cgg gac ctc aag tgt gtg gcc aat gga gac cag tgt gtc   627
Leu Leu Thr Arg Asp Leu Lys Cys Val Ala Asn Gly Asp Gln Cys Val
            190              195              200

tga cct                                                            633
 *
```

```
<210> 8
<211> 202
<212> PRT
<213> Mus musculus

<400> 8
Met Lys Pro Glu Thr Ala Gly Gly His Met Leu Leu Leu Leu Pro
1                   5                   10                  15
Leu Leu Leu Ala Ala Val Leu Thr Arg Thr Gln Ala Asp Pro Val Pro
            20                  25                  30
Arg Ala Thr Arg Leu Pro Val Glu Ala Lys Asp Cys His Ile Ala Gln
            35                  40                  45
Phe Lys Ser Leu Ser Pro Lys Glu Leu Gln Ala Phe Lys Lys Ala Lys
    50                  55                  60
Asp Ala Ile Glu Lys Arg Leu Leu Glu Lys Asp Leu Arg Cys Ser Ser
65                  70                  75                  80
His Leu Phe Pro Arg Ala Trp Asp Leu Lys Gln Leu Gln Val Gln Glu
                85                  90                  95
Arg Pro Lys Ala Leu Gln Ala Glu Val Ala Leu Thr Leu Lys Val Trp
            100                 105                 110
Glu Asn Met Thr Asp Ser Ala Leu Ala Thr Ile Leu Gly Gln Pro Leu
            115                 120                 125
His Thr Leu Ser His Ile His Ser Gln Leu Gln Thr Cys Thr Gln Leu
    130                 135                 140
Gln Ala Thr Ala Glu Pro Arg Ser Pro Ser Arg Arg Leu Ser Arg Trp
145                 150                 155                 160
Leu His Arg Leu Gln Glu Ala Gln Ser Lys Glu Thr Pro Gly Cys Leu
                165                 170                 175
```

```
Glu Ala Ser Val Thr Ser Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu
            180                 185                 190
Lys Cys Val Ala Asn Gly Asp Gln Cys Val
        195                 200


<210> 9
<211> 632
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (22)...(630)

<400> 9
tcacagaccc cggagagcaa c atg aag cca gaa aca gct ggg ggc cac atg      51
                         Met Lys Pro Glu Thr Ala Gly Gly His Met
                          1           5                      10

ctc ctc ctg ctg ttg cct ctg ctg ctg gcc gca gtg ctg aca aga acc      99
Leu Leu Leu Leu Leu Pro Leu Leu Leu Ala Ala Val Leu Thr Arg Thr
                15                  20                  25

caa gct gac cct gtc ccc agg gcc acc agg ctc cca gtg gaa gca aag     147
Gln Ala Asp Pro Val Pro Arg Ala Thr Arg Leu Pro Val Glu Ala Lys
                30                  35                  40

gat tgc cac att gct cag ttc aag tct ctg tcc cca aaa gag ctg cag     195
Asp Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Lys Glu Leu Gln
            45                  50                  55

gcc ttc aaa aag gcc aag ggt gcc atc gag aag agg ctg ctt gag aag     243
Ala Phe Lys Lys Ala Lys Gly Ala Ile Glu Lys Arg Leu Leu Glu Lys
        60                  65                  70

gac atg agg tgc agt tcc cac ctc atc tcc agg gcc tgg gac ctg aag     291
Asp Met Arg Cys Ser Ser His Leu Ile Ser Arg Ala Trp Asp Leu Lys
75                  80                  85                  90

cag ctg cag gtc caa gag cgc ccc aag gcc ttg cag gct gag gtg gcc     339
Gln Leu Gln Val Gln Glu Arg Pro Lys Ala Leu Gln Ala Glu Val Ala
                95                  100                 105

ctg acc ctg aag gtc tgg gag aac ata aat gac tca gcc ctg acc acc     387
Leu Thr Leu Lys Val Trp Glu Asn Ile Asn Asp Ser Ala Leu Thr Thr
                110                 115                 120

atc ctg ggc cag cct ctt cat aca ctg agc cac att cac tcc cag ctg     435
Ile Leu Gly Gln Pro Leu His Thr Leu Ser His Ile His Ser Gln Leu
            125                 130                 135

cag acc tgt aca cag ctt cag gcc aca gca gag ccc aag ccc ccg agt     483
Gln Thr Cys Thr Gln Leu Gln Ala Thr Ala Glu Pro Lys Pro Pro Ser
            140                 145                 150

cgc cgc ctc tcc cgc tgg ctg cac agg ctc cag gag gcc cag agc aag     531
Arg Arg Leu Ser Arg Trp Leu His Arg Leu Gln Glu Ala Gln Ser Lys
155                 160                 165                 170
```

```
gag act cct ggc tgc ctg gag gac tct gtc acc tcc aac ctg ttt caa    579
Glu Thr Pro Gly Cys Leu Glu Asp Ser Val Thr Ser Asn Leu Phe Gln
            175             180             185

ctg ctc ctc cgg gac ctc aag tgt gtg gcc agt gga gac cag tgt gtc    627
Leu Leu Leu Arg Asp Leu Lys Cys Val Ala Ser Gly Asp Gln Cys Val
            190             195             200

tga cc                                                             632
  *
```

```
<210> 10
<211> 202
<212> PRT
<213> Mus musculus

<400> 10
Met Lys Pro Glu Thr Ala Gly Gly His Met Leu Leu Leu Leu Pro
1               5               10              15
Leu Leu Leu Ala Ala Val Leu Thr Arg Thr Gln Ala Asp Pro Val Pro
            20              25              30
Arg Ala Thr Arg Leu Pro Val Glu Ala Lys Asp Cys His Ile Ala Gln
        35              40              45
Phe Lys Ser Leu Ser Pro Lys Glu Leu Gln Ala Phe Lys Lys Ala Lys
    50              55              60
Gly Ala Ile Glu Lys Arg Leu Leu Glu Lys Asp Met Arg Cys Ser Ser
65              70              75              80
His Leu Ile Ser Arg Ala Trp Asp Leu Lys Gln Leu Gln Val Gln Glu
            85              90              95
Arg Pro Lys Ala Leu Gln Ala Glu Val Ala Leu Thr Leu Lys Val Trp
            100             105             110
Glu Asn Ile Asn Asp Ser Ala Leu Thr Thr Ile Leu Gly Gln Pro Leu
        115             120             125
His Thr Leu Ser His Ile His Ser Gln Leu Gln Thr Cys Thr Gln Leu
    130             135             140
Gln Ala Thr Ala Glu Pro Lys Pro Pro Ser Arg Arg Leu Ser Arg Trp
145             150             155             160
Leu His Arg Leu Gln Glu Ala Gln Ser Lys Glu Thr Pro Gly Cys Leu
            165             170             175
Glu Asp Ser Val Thr Ser Asn Leu Phe Gln Leu Leu Leu Arg Asp Leu
            180             185             190
Lys Cys Val Ala Ser Gly Asp Gln Cys Val
            195             200
```

```
<210> 11
<211> 1563
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1563)

<221> misc_feature
<222> (0)...(0)
<223> IL-28RA
```

<400> 11

```
atg gcg ggg ccc gag cgc tgg ggc ccc ctg ctc ctg tgc ctg ctg cag    48
Met Ala Gly Pro Glu Arg Trp Gly Pro Leu Leu Leu Cys Leu Leu Gln
1               5                   10                  15

gcc gct cca ggg agg ccc cgt ctg gcc cct ccc cag aat gtg acg ctg    96
Ala Ala Pro Gly Arg Pro Arg Leu Ala Pro Pro Gln Asn Val Thr Leu
            20                  25                  30

ctc tcc cag aac ttc agc gtg tac ctg aca tgg ctc cca ggg ctt ggc    144
Leu Ser Gln Asn Phe Ser Val Tyr Leu Thr Trp Leu Pro Gly Leu Gly
        35                  40                  45

aac ccc cag gat gtg acc tat ttt gtg gcc tat cag agc tct ccc acc    192
Asn Pro Gln Asp Val Thr Tyr Phe Val Ala Tyr Gln Ser Ser Pro Thr
        50                  55                  60

cgt aga cgg tgg cgc gaa gtg gaa gag tgt gcg gga acc aag gag ctg    240
Arg Arg Arg Trp Arg Glu Val Glu Glu Cys Ala Gly Thr Lys Glu Leu
65                  70                  75                  80

cta tgt tct atg atg tgc ctg aag aaa cag gac ctg tac aac aag ttc    288
Leu Cys Ser Met Met Cys Leu Lys Lys Gln Asp Leu Tyr Asn Lys Phe
                85                  90                  95

aag gga cgc gtg cgg acg gtt tct ccc agc tcc aag tcc ccc tgg gtg    336
Lys Gly Arg Val Arg Thr Val Ser Pro Ser Ser Lys Ser Pro Trp Val
            100                 105                 110

gag tcc gaa tac ctg gat tac ctt ttt gaa gtg gag ccg gcc cca cct    384
Glu Ser Glu Tyr Leu Asp Tyr Leu Phe Glu Val Glu Pro Ala Pro Pro
            115                 120                 125

gtc ctg gtg ctc acc cag acg gag gag atc ctg agt gcc aat gcc acg    432
Val Leu Val Leu Thr Gln Thr Glu Glu Ile Leu Ser Ala Asn Ala Thr
        130                 135                 140

tac cag ctg ccc ccc tgc atg ccc cca ctg gat ctg aag tat gag gtg    480
Tyr Gln Leu Pro Pro Cys Met Pro Pro Leu Asp Leu Lys Tyr Glu Val
145                 150                 155                 160

gca ttc tgg aag gag ggg gcc gga aac aag acc cta ttt cca gtc act    528
Ala Phe Trp Lys Glu Gly Ala Gly Asn Lys Thr Leu Phe Pro Val Thr
                165                 170                 175

ccc cat ggc cag cca gtc cag atc act ctc cag cca gct gcc agc gaa    576
Pro His Gly Gln Pro Val Gln Ile Thr Leu Gln Pro Ala Ala Ser Glu
            180                 185                 190

cac cac tgc ctc agt gcc aga acc atc tac acg ttc agt gtc ccg aaa    624
His His Cys Leu Ser Ala Arg Thr Ile Tyr Thr Phe Ser Val Pro Lys
            195                 200                 205

tac agc aag ttc tct aag ccc acc tgc ttc ttg ctg gag gtc cca gaa    672
Tyr Ser Lys Phe Ser Lys Pro Thr Cys Phe Leu Leu Glu Val Pro Glu
        210                 215                 220

gcc aac tgg gct ttc ctg gtg ctg cca tcg ctt ctg ata ctg ctg tta    720
Ala Asn Trp Ala Phe Leu Val Leu Pro Ser Leu Leu Ile Leu Leu Leu
225                 230                 235                 240
```

11

```
gta att gcc gca ggg ggt gtg atc tgg aag acc ctc atg ggg aac ccc    768
Val Ile Ala Ala Gly Gly Val Ile Trp Lys Thr Leu Met Gly Asn Pro
                 245             250                 255

tgg ttt cag cgg gca aag atg cca cgg gcc ctg gac ttt tct gga cac    816
Trp Phe Gln Arg Ala Lys Met Pro Arg Ala Leu Asp Phe Ser Gly His
             260             265                 270

aca cac cct gtg gca acc ttt cag ccc agc aga cca gag tcc gtg aat    864
Thr His Pro Val Ala Thr Phe Gln Pro Ser Arg Pro Glu Ser Val Asn
             275             280                 285

gac ttg ttc ctc tgt ccc caa aag gaa ctg acc aga ggg gtc agg ccg    912
Asp Leu Phe Leu Cys Pro Gln Lys Glu Leu Thr Arg Gly Val Arg Pro
         290             295             300

acg cct cga gtc agg gcc cca gcc acc caa cag aca aga tgg aag aag    960
Thr Pro Arg Val Arg Ala Pro Ala Thr Gln Gln Thr Arg Trp Lys Lys
305             310             315                 320

gac ctt gca gag gac gaa gag gag gag gat gag gag gac aca gaa gat   1008
Asp Leu Ala Glu Asp Glu Glu Glu Glu Asp Glu Glu Asp Thr Glu Asp
                 325             330                 335

ggc gtc agc ttc cag ccc tac att gaa cca cct tct ttc ctg ggg caa   1056
Gly Val Ser Phe Gln Pro Tyr Ile Glu Pro Pro Ser Phe Leu Gly Gln
             340             345                 350

gag cac cag gct cca ggg cac tcg gag gct ggt ggg gtg gac tca ggg   1104
Glu His Gln Ala Pro Gly His Ser Glu Ala Gly Gly Val Asp Ser Gly
             355             360                 365

agg ccc agg gct cct ctg gtc cca agc gaa ggc tcc tct gct tgg gat   1152
Arg Pro Arg Ala Pro Leu Val Pro Ser Glu Gly Ser Ser Ala Trp Asp
         370             375             380

tct tca gac aga agc tgg gcc agc act gtg gac tcc tcc tgg gac agg   1200
Ser Ser Asp Arg Ser Trp Ala Ser Thr Val Asp Ser Ser Trp Asp Arg
385             390             395                 400

gct ggg tcc tct ggc tat ttg gct gag aag ggg cca ggc caa ggg ccg   1248
Ala Gly Ser Ser Gly Tyr Leu Ala Glu Lys Gly Pro Gly Gln Gly Pro
             405             410                 415

ggt ggg gat ggg cac caa gaa tct ctc cca cca cct gaa ttc tcc aag   1296
Gly Gly Asp Gly His Gln Glu Ser Leu Pro Pro Pro Glu Phe Ser Lys
             420             425                 430

gac tcg ggt ttc ctg gaa gag ctc cca gaa gat aac ctc tcc tcc tgg   1344
Asp Ser Gly Phe Leu Glu Glu Leu Pro Glu Asp Asn Leu Ser Ser Trp
             435             440                 445

gcc acc tgg ggc acc tta cca ccg gag ccg aat ctg gtc cct ggg gga   1392
Ala Thr Trp Gly Thr Leu Pro Pro Glu Pro Asn Leu Val Pro Gly Gly
         450             455             460

ccc cca gtt tct ctt cag aca ctg acc ttc tgc tgg gaa agc agc cct   1440
Pro Pro Val Ser Leu Gln Thr Leu Thr Phe Cys Trp Glu Ser Ser Pro
465             470             475                 480
```

```
gag gag gaa gag gag gcg agg gaa tca gaa att gag gac agc gat gcg   1488
Glu Glu Glu Glu Glu Ala Arg Glu Ser Glu Ile Glu Asp Ser Asp Ala
                485                 490                 495

ggc agc tgg ggg gct gag agc acc cag agg acc gag gac agg ggc cgg   1536
Gly Ser Trp Gly Ala Glu Ser Thr Gln Arg Thr Glu Asp Arg Gly Arg
                500                 505                 510

aca ttg ggg cat tac atg gcc agg tga                               1563
Thr Leu Gly His Tyr Met Ala Arg  *
            515                 520


<210> 12
<211> 520
<212> PRT
<213> Homo sapiens

<400> 12
Met Ala Gly Pro Glu Arg Trp Gly Pro Leu Leu Leu Cys Leu Leu Gln
1               5                   10                  15
Ala Ala Pro Gly Arg Pro Arg Leu Ala Pro Pro Gln Asn Val Thr Leu
                20                  25                  30
Leu Ser Gln Asn Phe Ser Val Tyr Leu Thr Trp Leu Pro Gly Leu Gly
            35                  40                  45
Asn Pro Gln Asp Val Thr Tyr Phe Val Ala Tyr Gln Ser Ser Pro Thr
        50                  55                  60
Arg Arg Arg Trp Arg Glu Val Glu Glu Cys Ala Gly Thr Lys Glu Leu
65                  70                  75                  80
Leu Cys Ser Met Met Cys Leu Lys Lys Gln Asp Leu Tyr Asn Lys Phe
                85                  90                  95
Lys Gly Arg Val Arg Thr Val Ser Pro Ser Ser Lys Ser Pro Trp Val
            100                 105                 110
Glu Ser Glu Tyr Leu Asp Tyr Leu Phe Glu Val Glu Pro Ala Pro Pro
        115                 120                 125
Val Leu Val Leu Thr Gln Thr Glu Glu Ile Leu Ser Ala Asn Ala Thr
    130                 135                 140
Tyr Gln Leu Pro Pro Cys Met Pro Pro Leu Asp Leu Lys Tyr Glu Val
145                 150                 155                 160
Ala Phe Trp Lys Glu Gly Ala Gly Asn Lys Thr Leu Phe Pro Val Thr
                165                 170                 175
Pro His Gly Gln Pro Val Gln Ile Thr Leu Gln Pro Ala Ala Ser Glu
            180                 185                 190
His His Cys Leu Ser Ala Arg Thr Ile Tyr Thr Phe Ser Val Pro Lys
        195                 200                 205
Tyr Ser Lys Phe Ser Lys Pro Thr Cys Phe Leu Leu Glu Val Pro Glu
    210                 215                 220
Ala Asn Trp Ala Phe Leu Val Leu Pro Ser Leu Leu Ile Leu Leu Leu
225                 230                 235                 240
Val Ile Ala Ala Gly Gly Val Ile Trp Lys Thr Leu Met Gly Asn Pro
                245                 250                 255
Trp Phe Gln Arg Ala Lys Met Pro Arg Ala Leu Asp Phe Ser Gly His
            260                 265                 270
Thr His Pro Val Ala Thr Phe Gln Pro Ser Arg Pro Glu Ser Val Asn
        275                 280                 285
Asp Leu Phe Leu Cys Pro Gln Lys Glu Leu Thr Arg Gly Val Arg Pro
    290                 295                 300
Thr Pro Arg Val Arg Ala Pro Ala Thr Gln Gln Thr Arg Trp Lys Lys
305                 310                 315                 320
Asp Leu Ala Glu Asp Glu Glu Glu Glu Asp Glu Glu Asp Thr Glu Asp
                325                 330                 335
```

```
Gly Val Ser Phe Gln Pro Tyr Ile Glu Pro Pro Ser Phe Leu Gly Gln
            340             345             350
Glu His Gln Ala Pro Gly His Ser Glu Ala Gly Gly Val Asp Ser Gly
        355             360             365
Arg Pro Arg Ala Pro Leu Val Pro Ser Glu Gly Ser Ser Ala Trp Asp
    370             375             380
Ser Ser Asp Arg Ser Trp Ala Ser Thr Val Asp Ser Ser Trp Asp Arg
385             390             395             400
Ala Gly Ser Ser Gly Tyr Leu Ala Glu Lys Gly Pro Gly Gln Gly Pro
                405             410             415
Gly Gly Asp Gly His Gln Glu Ser Leu Pro Pro Pro Glu Phe Ser Lys
            420             425             430
Asp Ser Gly Phe Leu Glu Glu Leu Pro Glu Asp Asn Leu Ser Ser Trp
        435             440             445
Ala Thr Trp Gly Thr Leu Pro Pro Glu Pro Asn Leu Val Pro Gly Gly
    450             455             460
Pro Pro Val Ser Leu Gln Thr Leu Thr Phe Cys Trp Glu Ser Ser Pro
465             470             475             480
Glu Glu Glu Glu Glu Ala Arg Glu Ser Glu Ile Glu Asp Ser Asp Ala
                485             490             495
Gly Ser Trp Gly Ala Glu Ser Thr Gln Arg Thr Glu Asp Arg Gly Arg
            500             505             510
Thr Leu Gly His Tyr Met Ala Arg
            515             520
```

```
<210> 13
<211> 1476
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1476)

<221> misc_feature
<222> (0)...(0)
<223> IL-28RA splice variant

<400> 13
atg gcg ggg ccc gag cgc tgg ggc ccc ctg ctc ctg tgc ctg ctg cag   48
Met Ala Gly Pro Glu Arg Trp Gly Pro Leu Leu Leu Cys Leu Leu Gln
1               5               10              15

gcc gct cca ggg agg ccc cgt ctg gcc cct ccc cag aat gtg acg ctg   96
Ala Ala Pro Gly Arg Pro Arg Leu Ala Pro Pro Gln Asn Val Thr Leu
            20              25              30

ctc tcc cag aac ttc agc gtg tac ctg aca tgg ctc cca ggg ctt ggc   144
Leu Ser Gln Asn Phe Ser Val Tyr Leu Thr Trp Leu Pro Gly Leu Gly
        35              40              45

aac ccc cag gat gtg acc tat ttt gtg gcc tat cag agc tct ccc acc   192
Asn Pro Gln Asp Val Thr Tyr Phe Val Ala Tyr Gln Ser Ser Pro Thr
    50              55              60

cgt aga cgg tgg cgc gaa gtg gaa gag tgt gcg gga acc aag gag ctg   240
Arg Arg Arg Trp Arg Glu Val Glu Glu Cys Ala Gly Thr Lys Glu Leu
65              70              75              80
```

14

```
cta tgt tct atg atg tgc ctg aag aaa cag gac ctg tac aac aag ttc    288
Leu Cys Ser Met Met Cys Leu Lys Lys Gln Asp Leu Tyr Asn Lys Phe
            85              90                  95

aag gga cgc gtg cgg acg gtt tct ccc agc tcc aag tcc ccc tgg gtg    336
Lys Gly Arg Val Arg Thr Val Ser Pro Ser Ser Lys Ser Pro Trp Val
            100             105                 110

gag tcc gaa tac ctg gat tac ctt ttt gaa gtg gag ccg gcc cca cct    384
Glu Ser Glu Tyr Leu Asp Tyr Leu Phe Glu Val Glu Pro Ala Pro Pro
            115             120                 125

gtc ctg gtg ctc acc cag acg gag gag atc ctg agt gcc aat gcc acg    432
Val Leu Val Leu Thr Gln Thr Glu Glu Ile Leu Ser Ala Asn Ala Thr
    130             135                 140

tac cag ctg ccc ccc tgc atg ccc cca ctg ttt ctg aag tat gag gtg    480
Tyr Gln Leu Pro Pro Cys Met Pro Pro Leu Phe Leu Lys Tyr Glu Val
145                 150                 155                 160

gca ttt tgg ggg ggg ggg gcc gga acc aag acc cta ttt cca gtc act    528
Ala Phe Trp Gly Gly Gly Ala Gly Thr Lys Thr Leu Phe Pro Val Thr
                    165                 170                 175

ccc cat ggc cag cca gtc cag atc act ctc cag cca gct gcc agc gaa    576
Pro His Gly Gln Pro Val Gln Ile Thr Leu Gln Pro Ala Ala Ser Glu
                180             185                 190

cac cac tgc ctc agt gcc aga acc atc tac acg ttc agt gtc ccg aaa    624
His His Cys Leu Ser Ala Arg Thr Ile Tyr Thr Phe Ser Val Pro Lys
            195             200                 205

tac agc aag ttc tct aag ccc acc tgc ttc ttg ctg gag gtc cca gaa    672
Tyr Ser Lys Phe Ser Lys Pro Thr Cys Phe Leu Leu Glu Val Pro Glu
    210             215                 220

gcc aac tgg gct ttc ctg gtg ctg cca tcg ctt ctg ata ctg ctg tta    720
Ala Asn Trp Ala Phe Leu Val Leu Pro Ser Leu Leu Ile Leu Leu Leu
225                 230                 235                 240

gta att gcc gca ggg ggt gtg atc tgg aag acc ctc atg ggg aac ccc    768
Val Ile Ala Ala Gly Gly Val Ile Trp Lys Thr Leu Met Gly Asn Pro
                    245                 250                 255

tgg ttt cag cgg gca aag atg cca cgg gcc ctg gaa ctg acc aga ggg    816
Trp Phe Gln Arg Ala Lys Met Pro Arg Ala Leu Glu Leu Thr Arg Gly
                260             265                 270

gtc agg ccg acg cct cga gtc agg gcc cca gcc acc caa cag aca aga    864
Val Arg Pro Thr Pro Arg Val Arg Ala Pro Ala Thr Gln Gln Thr Arg
            275             280                 285

tgg aag aag gac ctt gca gag gac gaa gag gag gag gat gag gag gac    912
Trp Lys Lys Asp Leu Ala Glu Asp Glu Glu Glu Glu Asp Glu Glu Asp
            290             295                 300

aca gaa gat ggc gtc agc ttc cag ccc tac att gaa cca cct tct ttc    960
Thr Glu Asp Gly Val Ser Phe Gln Pro Tyr Ile Glu Pro Pro Ser Phe
305                 310                 315                 320
```

```
ctg ggg caa gag cac cag gct cca ggg cac tcg gag gct ggt ggg gtg   1008
Leu Gly Gln Glu His Gln Ala Pro Gly His Ser Glu Ala Gly Gly Val
                325             330             335

gac tca ggg agg ccc agg gct cct ctg gtc cca agc gaa ggc tcc tct   1056
Asp Ser Gly Arg Pro Arg Ala Pro Leu Val Pro Ser Glu Gly Ser Ser
            340             345             350

gct tgg gat tct tca gac aga agc tgg gcc agc act gtg gac tcc tcc   1104
Ala Trp Asp Ser Ser Asp Arg Ser Trp Ala Ser Thr Val Asp Ser Ser
            355             360             365

tgg gac agg gct ggg tcc tct ggc tat ttg gct gag aag ggg cca ggc   1152
Trp Asp Arg Ala Gly Ser Ser Gly Tyr Leu Ala Glu Lys Gly Pro Gly
        370             375             380

caa ggg ccg ggt ggg gat ggg cac caa gaa tct ctc cca cca cct gaa   1200
Gln Gly Pro Gly Gly Asp Gly His Gln Glu Ser Leu Pro Pro Pro Glu
385             390             395             400

ttc tcc aag gac tcg ggt ttc ctg gaa gag ctc cca gaa gat aac ctc   1248
Phe Ser Lys Asp Ser Gly Phe Leu Glu Glu Leu Pro Glu Asp Asn Leu
            405             410             415

tcc tcc tgg gcc acc tgg ggc acc tta cca ccg gag ccg aat ctg gtc   1296
Ser Ser Trp Ala Thr Trp Gly Thr Leu Pro Pro Glu Pro Asn Leu Val
            420             425             430

cct ggg gga ccc cca gtt tct ctt cag aca ctg acc ttc tgc tgg gaa   1344
Pro Gly Gly Pro Pro Val Ser Leu Gln Thr Leu Thr Phe Cys Trp Glu
            435             440             445

agc agc cct gag gag gaa gag gag gcg agg gaa tca gaa att gag gac   1392
Ser Ser Pro Glu Glu Glu Glu Glu Ala Arg Glu Ser Glu Ile Glu Asp
    450             455             460

agc gat gcg ggc agc tgg ggg gct gag agc acc cag agg acc gag gac   1440
Ser Asp Ala Gly Ser Trp Gly Ala Glu Ser Thr Gln Arg Thr Glu Asp
465             470             475             480

agg ggc cgg aca ttg ggg cat tac atg gcc agg tga                   1476
Arg Gly Arg Thr Leu Gly His Tyr Met Ala Arg *
            485             490
```

<210> 14
<211> 491
<212> PRT
<213> Homo sapiens

<400> 14
```
Met Ala Gly Pro Glu Arg Trp Gly Pro Leu Leu Leu Cys Leu Leu Gln
1               5               10              15
Ala Ala Pro Gly Arg Pro Arg Leu Ala Pro Pro Gln Asn Val Thr Leu
            20              25              30
Leu Ser Gln Asn Phe Ser Val Tyr Leu Thr Trp Leu Pro Gly Leu Gly
        35              40              45
Asn Pro Gln Asp Val Thr Tyr Phe Val Ala Tyr Gln Ser Ser Pro Thr
    50              55              60
Arg Arg Arg Trp Arg Glu Val Glu Glu Cys Ala Gly Thr Lys Glu Leu
65              70              75              80
```

16

```
Leu Cys Ser Met Met Cys Leu Lys Lys Gln Asp Leu Tyr Asn Lys Phe
            85                  90                  95
Lys Gly Arg Val Arg Thr Val Ser Pro Ser Ser Lys Ser Pro Trp Val
            100             105             110
Glu Ser Glu Tyr Leu Asp Tyr Leu Phe Glu Val Glu Pro Ala Pro Pro
        115                 120             125
Val Leu Val Leu Thr Gln Thr Glu Glu Ile Leu Ser Ala Asn Ala Thr
    130             135             140
Tyr Gln Leu Pro Pro Cys Met Pro Pro Leu Phe Leu Lys Tyr Glu Val
145             150             155             160
Ala Phe Trp Gly Gly Gly Ala Gly Thr Lys Thr Leu Phe Pro Val Thr
                165             170             175
Pro His Gly Gln Pro Val Gln Ile Thr Leu Gln Pro Ala Ala Ser Glu
                180             185             190
His His Cys Leu Ser Ala Arg Thr Ile Tyr Thr Phe Ser Val Pro Lys
        195                 200             205
Tyr Ser Lys Phe Ser Lys Pro Thr Cys Phe Leu Leu Glu Val Pro Glu
    210             215             220
Ala Asn Trp Ala Phe Leu Val Leu Pro Ser Leu Leu Ile Leu Leu Leu
225             230             235             240
Val Ile Ala Ala Gly Val Ile Trp Lys Thr Leu Met Gly Asn Pro
                245             250             255
Trp Phe Gln Arg Ala Lys Met Pro Arg Ala Leu Glu Leu Thr Arg Gly
                260             265             270
Val Arg Pro Thr Pro Arg Val Arg Ala Pro Ala Thr Gln Gln Thr Arg
        275             280             285
Trp Lys Lys Asp Leu Ala Glu Asp Glu Glu Glu Asp Glu Glu Asp
    290             295             300
Thr Glu Asp Gly Val Ser Phe Gln Pro Tyr Ile Glu Pro Pro Ser Phe
305             310             315             320
Leu Gly Gln Glu His Gln Ala Pro Gly His Ser Glu Ala Gly Gly Val
                325             330             335
Asp Ser Gly Arg Pro Arg Ala Pro Leu Val Pro Ser Glu Gly Ser Ser
            340             345             350
Ala Trp Asp Ser Ser Asp Arg Ser Trp Ala Ser Thr Val Asp Ser Ser
        355             360             365
Trp Asp Arg Ala Gly Ser Ser Gly Tyr Leu Ala Glu Lys Gly Pro Gly
    370             375             380
Gln Gly Pro Gly Gly Asp Gly His Gln Glu Ser Leu Pro Pro Pro Glu
385             390             395             400
Phe Ser Lys Asp Ser Gly Phe Leu Glu Glu Leu Pro Glu Asp Asn Leu
            405             410             415
Ser Ser Trp Ala Thr Trp Gly Thr Leu Pro Pro Glu Pro Asn Leu Val
        420             425             430
Pro Gly Gly Pro Pro Val Ser Leu Gln Thr Leu Thr Phe Cys Trp Glu
        435             440             445
Ser Ser Pro Glu Glu Glu Glu Glu Ala Arg Glu Ser Glu Ile Glu Asp
    450             455             460
Ser Asp Ala Gly Ser Trp Gly Ala Glu Ser Thr Gln Arg Thr Glu Asp
465             470             475             480
Arg Gly Arg Thr Leu Gly His Tyr Met Ala Arg
                485             490
```

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<210> 15
<211> 674
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(636)
```

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<221> misc_feature
<222> (0)...(0)
<223> IL-28RA soluble variant

<400> 15
atg gcg ggg ccc gag cgc tgg ggc ccc ctg ctc ctg tgc ctg ctg cag    48
Met Ala Gly Pro Glu Arg Trp Gly Pro Leu Leu Leu Cys Leu Leu Gln
1               5                   10                  15

gcc gct cca ggg agg ccc cgt ctg gcc cct ccc cag aat gtg acg ctg    96
Ala Ala Pro Gly Arg Pro Arg Leu Ala Pro Pro Gln Asn Val Thr Leu
            20                  25                  30

ctc tcc cag aac ttc agc gtg tac ctg aca tgg ctc cca ggg ctt ggc   144
Leu Ser Gln Asn Phe Ser Val Tyr Leu Thr Trp Leu Pro Gly Leu Gly
        35                  40                  45

aac ccc cag gat gtg acc tat ttt gtg gcc tat cag agc tct ccc acc   192
Asn Pro Gln Asp Val Thr Tyr Phe Val Ala Tyr Gln Ser Ser Pro Thr
        50                  55                  60

cgt aga cgg tgg cgc gaa gtg gaa gag tgt gcg gga acc aag gag ctg   240
Arg Arg Arg Trp Arg Glu Val Glu Glu Cys Ala Gly Thr Lys Glu Leu
65                  70                  75                  80

cta tgt tct atg atg tgc ctg aag aaa cag gac ctg tac aac aag ttc   288
Leu Cys Ser Met Met Cys Leu Lys Lys Gln Asp Leu Tyr Asn Lys Phe
                85                  90                  95

aag gga cgc gtg cgg acg gtt tct ccc agc tcc aag tcc ccc tgg gtg   336
Lys Gly Arg Val Arg Thr Val Ser Pro Ser Ser Lys Ser Pro Trp Val
            100                 105                 110

gag tcc gaa tac ctg gat tac ctt ttt gaa gtg gag ccg gcc cca cct   384
Glu Ser Glu Tyr Leu Asp Tyr Leu Phe Glu Val Glu Pro Ala Pro Pro
        115                 120                 125

gtc ctg gtg ctc acc cag acg gag gag atc ctg agt gcc aat gcc acg   432
Val Leu Val Leu Thr Gln Thr Glu Glu Ile Leu Ser Ala Asn Ala Thr
        130                 135                 140

tac cag ctg ccc ccc tgc atg ccc cca ctg gat ctg aag tat gag gtg   480
Tyr Gln Leu Pro Pro Cys Met Pro Pro Leu Asp Leu Lys Tyr Glu Val
145                 150                 155                 160

gca ttc tgg aag gag ggg gcc gga aac aag gtg gga agc tcc ttt cct   528
Ala Phe Trp Lys Glu Gly Ala Gly Asn Lys Val Gly Ser Ser Phe Pro
                165                 170                 175

gcc ccc agg cta ggc ccg ctc ctc cac ccc ttc tta ctc agg ttc ttc   576
Ala Pro Arg Leu Gly Pro Leu Leu His Pro Phe Leu Leu Arg Phe Phe
            180                 185                 190

tca ccc tcc cag cct gct cct gca ccc ctc ctc cag gaa gtc ttc cct   624
Ser Pro Ser Gln Pro Ala Pro Ala Pro Leu Leu Gln Glu Val Phe Pro
            195                 200                 205

gta cac tcc tga cttctggcag tcagccctaa taaaatctga tcaaagta        674
Val His Ser *
            210
```

```
<210> 16
<211> 211
<212> PRT
<213> Homo sapiens

<400> 16
Met Ala Gly Pro Glu Arg Trp Gly Pro Leu Leu Leu Cys Leu Leu Gln
1               5                   10                  15
Ala Ala Pro Gly Arg Pro Arg Leu Ala Pro Pro Gln Asn Val Thr Leu
            20                  25                  30
Leu Ser Gln Asn Phe Ser Val Tyr Leu Thr Trp Leu Pro Gly Leu Gly
        35                  40                  45
Asn Pro Gln Asp Val Thr Tyr Phe Val Ala Tyr Gln Ser Ser Pro Thr
        50                  55                  60
Arg Arg Arg Trp Arg Glu Val Glu Glu Cys Ala Gly Thr Lys Glu Leu
65                  70                  75                  80
Leu Cys Ser Met Met Cys Leu Lys Lys Gln Asp Leu Tyr Asn Lys Phe
                85                  90                  95
Lys Gly Arg Val Arg Thr Val Ser Pro Ser Ser Lys Ser Pro Trp Val
            100                 105                 110
Glu Ser Glu Tyr Leu Asp Tyr Leu Phe Glu Val Glu Pro Ala Pro Pro
        115                 120                 125
Val Leu Val Leu Thr Gln Thr Glu Glu Ile Leu Ser Ala Asn Ala Thr
    130                 135                 140
Tyr Gln Leu Pro Pro Cys Met Pro Pro Leu Asp Leu Lys Tyr Glu Val
145                 150                 155                 160
Ala Phe Trp Lys Glu Gly Ala Gly Asn Lys Val Gly Ser Ser Phe Pro
                165                 170                 175
Ala Pro Arg Leu Gly Pro Leu Leu His Pro Phe Leu Leu Arg Phe Phe
            180                 185                 190
Ser Pro Ser Gln Pro Ala Pro Ala Pro Leu Leu Gln Glu Val Phe Pro
            195                 200                 205
Val His Ser
            210


<210> 17
<211> 734
<212> DNA
<213> Homo sapiens

<220>
<221> sig_peptide
<222> (53)...(127)

<221> mat_peptide
<222> (128)...(655)

<221> CDS
<222> (53)...(655)

<400> 17
tgggtgacag cctcagagtg tttcttctgc tgacaaagac cagagatcag ga atg aaa  58
                                                             Met Lys
                                                             -25

cta gac atg act ggg gac tgc acg cca gtg ctg gtg ctg atg gcc gca  106
Leu Asp Met Thr Gly Asp Cys Thr Pro Val Leu Val Leu Met Ala Ala
        -20             -15                 -10
```

```
gtg ctg acc gtg act gga gca gtt cct gtc gcc agg ctc cac ggg gct      154
Val Leu Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu His Gly Ala
        -5                  1                5

ctc ccg gat gca agg ggc tgc cac ata gcc cag ttc aag tcc ctg tct      202
Leu Pro Asp Ala Arg Gly Cys His Ile Ala Gln Phe Lys Ser Leu Ser
 10                  15                  20                  25

cca cag gag ctg cag gcc ttt aag agg gcc aaa gat gcc tta gaa gag      250
Pro Gln Glu Leu Gln Ala Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu
            30                  35                  40

tcg ctt ctg ctg aag gac tgc agg tgc cac tcc cgc ctc ttc ccc agg      298
Ser Leu Leu Leu Lys Asp Cys Arg Cys His Ser Arg Leu Phe Pro Arg
            45                  50                  55

acc tgg gac ctg agg cag ctg cag gtg agg gag cgc ccc atg gct ttg      346
Thr Trp Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Met Ala Leu
            60                  65                  70

gag gct gag ctg gcc ctg acg ctg aag gtt ctg gag gcc acc gct gac      394
Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr Ala Asp
        75                  80                  85

act gac cca gcc ctg gtg gac gtc ttg gac cag ccc ctt cac acc ctg      442
Thr Asp Pro Ala Leu Val Asp Val Leu Asp Gln Pro Leu His Thr Leu
 90                  95                  100                 105

cac cat atc ctc tcc cag ttc cgg gcc tgt atc cag cct cag ccc acg      490
His His Ile Leu Ser Gln Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr
            110                 115                 120

gca ggg ccc agg acc cgg ggc cgc ctc cac cat tgg ctg tac cgg ctc      538
Ala Gly Pro Arg Thr Arg Gly Arg Leu His His Trp Leu Tyr Arg Leu
            125                 130                 135

cag gag gcc cca aaa aag gag tcc cct ggc tgc ctc gag gcc tct gtc      586
Gln Glu Ala Pro Lys Lys Glu Ser Pro Gly Cys Leu Glu Ala Ser Val
            140                 145                 150

acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctg aat tgt gtt gcc      634
Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Asn Cys Val Ala
            155                 160                 165

agt ggg gac ctg tgt gtc tga ccctcccacc agtcatgcaa cctgagattt         685
Ser Gly Asp Leu Cys Val *
170                 175

tatttataaa ttagccactt gtcttaattt attgccaccc agtcgctat              734
```

<210> 18
<211> 200
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> (1)...(25)

<400> 18
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Met Lys Leu Asp Met Thr Gly Asp Cys Thr Pro Val Leu Val Leu Met
-25                 -20                 -15                 -10
```

```
Ala Ala Val Leu Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu His
            -5                  1           5
Gly Ala Leu Pro Asp Ala Arg Gly Cys His Ile Ala Gln Phe Lys Ser
        10          15              20
Leu Ser Pro Gln Glu Leu Gln Ala Phe Lys Arg Ala Lys Asp Ala Leu
    25          30              35
Glu Glu Ser Leu Leu Leu Lys Asp Cys Arg Cys His Ser Arg Leu Phe
40              45              50                      55
Pro Arg Thr Trp Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Met
            60              65              70
Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr
        ' 75              80                  85
Ala Asp Thr Asp Pro Ala Leu Val Asp Val Leu Asp Gln Pro Leu His
        90              95              100
Thr Leu His His Ile Leu Ser Gln Phe Arg Ala Cys Ile Gln Pro Gln
    105             110             115
Pro Thr Ala Gly Pro Arg Thr Arg Gly Arg Leu His His Trp Leu Tyr
120             125             130                     135
Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Pro Gly Cys Leu Glu Ala
            140             145             150
Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Asn Cys
            155             160                 165
Val Ala Ser Gly Asp Leu Cys Val
            170             175


<210> 19
<211> 856
<212> DNA
<213> Homo sapiens

<220>
<221> sig_peptide
<222> (98)...(154)

<221> mat_peptide
<222> (155)...(700)

<221> CDS
<222> (98)...(700)

<400> 19
aattaccttt tcactttaca cacatcatct tggattgccc attttgcgtg gctaaaaagc 60
agagccatgc cgctggggaa gcagttgcga tttagcc atg gct gca gct tgg acc 115
                                      Met Ala Ala Ala Trp Thr
                                                          -15

gtg gtg ctg gtg act ttg gtg cta ggc ttg gcc gtg gca ggc cct gtc   163
Val Val Leu Val Thr Leu Val Leu Gly Leu Ala Val Ala Gly Pro Val
            -10             -5                  1

ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac att ggc agg   211
Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg
    5               10              15

ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag aag gcc agg   259
Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg
20              25              30                      35

gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc tct   307
Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser
                40              45              50
```

```
cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg gag   355
Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu
            55              60                  65

cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc ctg   403
Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu
            70              75                  80

gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac cag ccc ctt   451
Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu
        85              90                  95

cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc cag cct   499
His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro
100             105                 110                 115

cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg ctg   547
Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu
                120             125                 130

cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc tgc ctg gag   595
His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu
            135             140                 145

gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc aaa   643
Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys
        150             155                 160

tat gtg gcc gat ggg aac ctg tgt ctg aga acg tca acc cac cct gag   691
Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser Thr His Pro Glu
        165             170                 175

tcc acc tga caccccacac cttatttatg cgctgagccc tactccttcc          740
Ser Thr *
180

ttaatttatt tcctctcacc ctttatttat gaagctgcag ccctgactga gacatagggc 800
tgagtttatt gttttacttt tatacattat gcacaaataa acaacaagga attgga      856
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```
<210> 20
<211> 200
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> (1)...(19)

<400> 20
Met Ala Ala Ala Trp Thr Val Val Leu Val Thr Leu Val Leu Gly Leu
                -15             -10                     -5
Ala Val Ala Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys
                1               5               10
Gly Cys His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala
        15              20              25
Ser Phe Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys
30              35              40                  45
Asn Trp Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg
                50              55              60
Leu Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala
            65              70                  75
```

22

```
Leu Thr Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp
        80                  85                  90
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
        95              100                 105
Gln Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly
110                 115                 120                 125
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
            130                 135                 140
Ser Ala Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
            145                 150                 155
Leu Thr Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg
        160                 165                 170
Thr Ser Thr His Pro Glu Ser Thr
        175                 180
```

```
<210> 21
<211> 734
<212> DNA
<213> Homo sapiens

<220>
<221> sig_peptide
<222> (53)...(127)

<221> mat_peptide
<222> (128)...(655)

<221> CDS
<222> (53)...(655)

<400> 21
tgggtgacag cctcagagtg tttcttctgc tgacaaagac cagagatcag ga atg aaa  58
                                                            Met Lys
                                                            -25
```

```
cta gac atg acc ggg gac tgc atg cca gtg ctg gtg ctg atg gcc gca  106
Leu Asp Met Thr Gly Asp Cys Met Pro Val Leu Val Leu Met Ala Ala
        -20                 -15                 -10

gtg ctg acc gtg act gga gca gtt cct gtc gcc agg ctc cgc ggg gct  154
Val Leu Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu Arg Gly Ala
        -5                  1                   5

ctc ccg gat gca agg ggc tgc cac ata gcc cag ttc aag tcc ctg tct  202
Leu Pro Asp Ala Arg Gly Cys His Ile Ala Gln Phe Lys Ser Leu Ser
10                  15                  20                  25

cca cag gag ctg cag gcc ttt aag agg gcc aaa gat gcc tta gaa gag  250
Pro Gln Glu Leu Gln Ala Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu
                30                  35                  40

tcg ctt ctg ctg aag gac tgc aag tgc cgc tcc cgc ctc ttc ccc agg  298
Ser Leu Leu Leu Lys Asp Cys Lys Cys Arg Ser Arg Leu Phe Pro Arg
                45                  50                  55

acc tgg gac ctg agg cag ctg cag gtg agg gag cgc ccc gtg gct ttg  346
Thr Trp Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Val Ala Leu
            60                  65                  70
```

```
gag gct gag ctg gcc ctg acg ctg aag gtt ctg gag gcc acc gct gac     394
Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr Ala Asp
    75              80              85


act gac cca gcc ctg ggg gat gtc ttg gac cag ccc ctt cac acc ctg     442
Thr Asp Pro Ala Leu Gly Asp Val Leu Asp Gln Pro Leu His Thr Leu
90              95              100             105


cac cat atc ctc tcc cag ctc cgg gcc tgt atc cag cct cag ccc acg     490
His His Ile Leu Ser Gln Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr
            110             115             120


gca ggg ccc agg acc cgg ggc cgc ctc cac cat tgg ctg cac cgg ctc     538
Ala Gly Pro Arg Thr Arg Gly Arg Leu His His Trp Leu His Arg Leu
            125             130             135


cag gag gcc cca aaa aag gag tcc cct ggc tgc ctc gag gcc tct gtc     586
Gln Glu Ala Pro Lys Lys Glu Ser Pro Gly Cys Leu Glu Ala Ser Val
            140             145             150


acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctg aat tgt gtt gcc     634
Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Asn Cys Val Ala
    155             160             165


agc ggg gac ctg tgt gtc tga cccttccgcc agtcatgcaa cctgagattt        685
Ser Gly Asp Leu Cys Val *
170             175


tatttataaa ttagccactt ggcttaattt attgccaccc agtcgctat              734
```

<210> 22
<211> 200
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> (1)...(25)

<400> 22
```
Met Lys Leu Asp Met Thr Gly Asp Cys Met Pro Val Leu Val Leu Met
-25             -20             -15             -10
Ala Ala Val Leu Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu Arg
            -5              1               5
Gly Ala Leu Pro Asp Ala Arg Gly Cys His Ile Ala Gln Phe Lys Ser
            10              15              20
Leu Ser Pro Gln Glu Leu Gln Ala Phe Lys Arg Ala Lys Asp Ala Leu
    25              30              35
Glu Glu Ser Leu Leu Leu Lys Asp Cys Lys Cys Arg Ser Arg Leu Phe
40              45              50              55
Pro Arg Thr Trp Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Val
            60              65              70
Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr
            75              80              85
Ala Asp Thr Asp Pro Ala Leu Gly Asp Val Leu Asp Gln Pro Leu His
            90              95              100
Thr Leu His His Ile Leu Ser Gln Leu Arg Ala Cys Ile Gln Pro Gln
    105             110             115
Pro Thr Ala Gly Pro Arg Thr Arg Gly Arg Leu His His Trp Leu His
120             125             130             135
Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Pro Gly Cys Leu Glu Ala
            140             145             150
```

```
Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Asn Cys
            155                 160                 165
Val Ala Ser Gly Asp Leu Cys Val
        170             175


<210> 23
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28A mutant C48S

<221> CDS
<222> (1)...(528)

<400> 23
gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc tgc     48
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys
 1               5                   10                  15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt     96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
            20                  25                  30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac tcc    144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Ser
        35                  40                  45

agg tgc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg    192
Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
    50                  55                  60

cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg acg    240
Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg gac    288
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val Asp
                85                  90                  95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ttc    336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Phe
            100                 105                 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc    384
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
            115                 120                 125

cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag gag    432
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
        130                 135                 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc    480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160

ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc tga    528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val *
                165                 170                 175
```

```
<210> 24
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-28A mutant C48S

<400> 24
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys
1               5                   10                  15
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
            20                  25                  30
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Ser
        35                  40                  45
Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
    50                  55                  60
Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val Asp
                85                  90                  95
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Phe
                100                 105                 110
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
            115                 120                 125
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
        130                 135                 140
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175


<210> 25
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C49S

<221> CDS
<222> (1)...(531)

<400> 25
atg gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc   48
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1               5                   10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc   96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
                20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac  144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
            35                  40                  45

tcc agg tgc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag  192
Ser Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50                  55                  60
```

```
ctg cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg      240
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
 65               70              75               80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg      288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
             85              90              95

gac gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag      336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100             105             110

ttc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg      384
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
            115             120             125

ggc cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag      432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
        130             135             140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc      480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145             150             155             160

ctc ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc      528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
            165             170             175

tga                                                                  531
 *
```

```
<210> 26
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C49S

<400> 26
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
 1               5               10              15
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20              25              30
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
        35              40              45
Ser Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50              55              60
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65              70              75              80
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
            85              90              95
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100             105             110
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
            115             120             125
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
        130             135             140
```

```
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145             150                 155                 160
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175
```

<210> 27
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28A mutant C50S

<221> CDS
<222> (1)...(528)

<400> 27
```
gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc tgc      48
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys
1                5                   10                  15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt      96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
            20                  25                  30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac tgc     144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Cys
            35                  40                  45

agg tcc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg     192
Arg Ser His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
    50                  55                  60

cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg acg     240
Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg gac     288
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val Asp
                85                  90                  95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ttc     336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Phe
            100                 105                 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc     384
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
            115                 120                 125

cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag gag     432
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc     480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160

ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc tga     528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val *
                165                 170                 175
```

```
<210> 28
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-28A mutant C50S

<400> 28
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys
1               5                   10                  15
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
            20                  25                  30
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Cys
        35                  40                  45
Arg Ser His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
    50                  55                  60
Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val Asp
                85                  90                  95
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Phe
                100                 105                 110
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
            115                 120                 125
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175


<210> 29
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C51S

<221> CDS
<222> (1)...(531)

<400> 29
atg gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc      48
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1               5                   10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc      96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
                20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac     144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
            35                  40                  45

tgc agg tcc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag     192
Cys Arg Ser His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50                  55                  60
```

```
ctg cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65              70              75              80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
                85              90              95

gac gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100             105             110

ttc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115             120             125

ggc cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130             135             140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145             150             155             160

ctc ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165             170             175

tga                                                               531
*
```

```
<210> 30
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C51S

<400> 30
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1               5               10              15
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20              25              30
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
        35              40              45
Cys Arg Ser His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50              55              60
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65              70              75              80
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
                85              90              95
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100             105             110
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115             120             125
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130             135             140
```

```
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145               150               155               160
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165               170               175
```

<210> 31
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 mutant C171S

<221> CDS
<222> (1)...(546)

<400> 31
```
ggt ccg gtt ccg acc tct aaa cca acc acc act ggt aaa ggt tgc cac      48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His
1               5                   10                  15

atc ggt cgt ttc aaa tct ctg tct ccg cag gaa ctg gct tct ttc aaa      96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
                20                  25                  30

aaa gct cgt gac gct ctg gaa gaa tct ctg aaa ctg aaa aac tgg tct     144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
            35                  40                  45

tgc tct tct ccg gtt ttc ccg ggt aac tgg gat ctg cgt ctg ctg cag     192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
        50                  55                  60

gtt cgt gaa cgt ccg gtt gct ctg gaa gct gaa ctg gct ctg acc ctg     240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aaa gtt ctg gaa gct gct gca ggt cct gct ctg gaa gat gtt ctg gat     288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccg ctg cac act ctg cac cac atc ctg tct cag ctg cag gct tgc     336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

att caa ccg caa ccg acc gct ggt ccg cgt ccg cgt ggt cgt ctg cac     384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
            115                 120                 125

cac tgg ctg cat cgt ctg cag gaa gct ccg aaa aaa gaa tct gct ggt     432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
        130                 135                 140

tgc ctg gaa gct tct gtt acc ttc aac ctg ttc cgt ctg ctg acc cgt     480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gat ctg aaa tac gtt gct gat ggt aac ctg tct ctg cgt acc tct acc     528
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Ser Leu Arg Thr Ser Thr
                165                 170                 175
```

31

```
cat ccg gaa tct acc taa                                                           546
His Pro Glu Ser Thr  *
                 180
```

```
<210> 32
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 mutant C171S

<400> 32
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His
1               5                   10                  15
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
            35                  40                  45
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
            115                 120                 125
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Ser Leu Arg Thr Ser Thr
                165                 170                 175
His Pro Glu Ser Thr
                180
```

```
<210> 33
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-29 mutant C172S

<221> CDS
<222> (1)...(549)

<400> 33
atg ggt ccg gtt ccg acc tct aaa cca acc acc act ggt aaa ggt tgc    48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
1               5                   10                  15

cac atc ggt cgt ttc aaa tct ctg tct ccg cag gaa ctg gct tct ttc    96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30
```

```
aaa aaa gct cgt gac gct ctg gaa gaa tct ctg aaa ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35              40                  45

tct tgc tct tct ccg gtt ttc ccg ggt aac tgg gat ctg cgt ctg ctg   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
        50              55                  60

cag gtt cgt gaa cgt ccg gtt gct ctg gaa gct gaa ctg gct ctg acc   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65              70                  75                      80

ctg aaa gtt ctg gaa gct gct gca ggt cct gct ctg gaa gat gtt ctg   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gat cag ccg ctg cac act ctg cac cac atc ctg tct cag ctg cag gct   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgc att caa ccg caa ccg acc gct ggt ccg cgt ccg cgt ggt cgt ctg   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
            115                 120                 125

cac cac tgg ctg cat cgt ctg cag gaa gct ccg aaa aaa gaa tct gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
        130                 135                 140

ggt tgc ctg gaa gct tct gtt acc ttc aac ctg ttc cgt ctg ctg acc   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145             150                 155                 160

cgt gat ctg aaa tac gtt gct gat ggt aac ctg tct ctg cgt acc tct   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Ser Leu Arg Thr Ser
            165                 170                 175

acc cat ccg gaa tct acc taa                                        549
Thr His Pro Glu Ser Thr *
            180
```

```
<210> 34
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-29 mutant C172S

<400> 34
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
1               5               10                  15
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35              40                  45
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
        50              55                  60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65              70                  75                      80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95
```

```
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
        100                 105                 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
    115                 120                 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Ser Leu Arg Thr Ser
                165                 170                 175
Thr His Pro Glu Ser Thr
                180
```

```
<210> 35
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-28A

<221> CDS
<222> (1)...(531)

<400> 35
atg gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc    48
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1               5                   10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc    96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
            35                  40                  45

tgc agg tgc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Cys Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
        50                  55                  60

ctg cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
                85                  90                  95

gac gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ttc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
            115                 120                 125

ggc cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
        130                 135                 140
```

34

```
gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145             150             155             160

ctc ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165             170             175

tga                                                                531
 *
```

```
<210> 36
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28A

<400> 36
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
 1               5                  10                  15
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20                  25                  30
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
            35                  40                  45
Cys Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50                  55                  60
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
                85                  90                  95
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
                100                 105                 110
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
            115                 120                 125
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175
```

```
<210> 37
<211> 621
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-29

<221> CDS
<222> (1)...(549)

<400> 37
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15
```

```
cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc    96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20              25              30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
            35              40              45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
        50              55              60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65              70              75              80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85              90              95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100             105             110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
            115             120             125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
        130             135             140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145             150             155             160

cga gac ctc aaa tat gtg gcc gat ggg aac ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
                165             170             175

acc cac cct gag tcc acc tga cacccacac cttatttatg cgctgagccc       579
Thr His Pro Glu Ser Thr *
            180

tactccttcc ttaatttatt tcctctcacc ctttatttat ga                   621
```

```
<210> 38
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-29

<400> 38
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
1               5               10              15
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20              25              30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
            35              40              45
```

```
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55              60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70              75                  80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85              90                  95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100             105             110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115             120             125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130             135             140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145             150             155             160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
            165             170             175
Thr His Pro Glu Ser Thr
            180
```

```
<210> 39
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-28B

<221> CDS
<222> (1)...(531)

<400> 39
atg gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc    48
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
1               5                   10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc    96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
                20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
            35                  40                  45

tgc aag tgc cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Cys Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
        50                  55                  60

ctg cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg ggg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly
                85                  90                  95

gat gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100             105             110
```

37

```
ctc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg       384
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115             120             125

ggc cgc ctc cac cat tgg ctg cac cgg ctc cag gag gcc cca aaa aag       432
Gly Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys
        130             135             140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc       480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145             150             155             160

ctc ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc       528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165             170             175

tga                                                                   531
 *
```

<210> 40
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28B

<400> 40
```
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
 1               5               10              15
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20              25              30
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
        35              40              45
Cys Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50              55              60
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65              70              75              80
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly
            85              90              95
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100             105             110
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115             120             125
Gly Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys
        130             135             140
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145             150             155             160
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165             170             175
```